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(54) **COMPOSITIONS WITH MODULATING AGENTS**

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(58) **Field of Classification Search**

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(57) **ABSTRACT**

The present invention relates to a waterless composition and foam as a vehicle in which an active pharmaceutical or cosmetic agent, when added is stable or stabilized by or its destabilization is impeded by the presence of a modulating agent. The pharmaceutical or cosmetic composition and foam, includes: a waterless solvent, a modulating agent and one or more active pharmaceutical or cosmetic agents. The present invention also relates to a method of treatment administering the waterless composition and foam.

46 Claims, No Drawings

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COMPOSITIONS WITH MODULATING AGENTS

CROSS REFERENCE TO RELATED APPLICATIONS

This application claims priority under 35 U.S.C. § 119 (e) to U.S. Provisional Application Ser. No. 60/861,620, filed Nov. 29, 2006, which is hereby incorporated by reference.

This application is a continuation of U.S. patent application Ser. No. 11/947,751, filed on Nov. 29, 2007, and issued as U.S. Pat. No. 8,795,693 on Aug. 5, 2014, which is a continuation-in-part application of co-pending U.S. patent application Ser. No. 10/835,505, filed on Apr. 28, 2004, which claims the benefit of priority under 35 U.S.C. § 119(e) to U.S. Patent Application Ser. No. 60/530,015, filed on Dec. 16, 2003, and U.S. Patent Application Ser. No. 60/492,385, filed on Aug. 4, 2003, all hereby incorporated in their entirety by reference.

This application is a continuation of U.S. patent application Ser. No. 11/947,751, filed on Nov. 29, 2007, and issued as U.S. Pat. No. 8,795,693 on Aug. 5, 2014, which is a continuation in part of U.S. patent application Ser. No. 11/430,599, filed on May 9, 2006, which claims the benefit under 35 U.S.C. § 119(e) of U.S. Provisional Patent Application No. 60/784,793, filed on Mar. 21, 2006, and of U.S. Provisional Patent Application No. 60/679,020, filed on May 9, 2005, which are herein incorporated by reference in their entirety.

BACKGROUND

This invention relates to pharmaceutical and cosmetic compositions, particularly waterless compositions.

External topical administration is an important route for the administration of drugs in disease treatment. Many groups of drugs, including, for example, antibiotic, anti-fungal, anti-inflammatory, anesthetic, analgesic, anti-allergic, corticosteroid, anti-psoriasis, retinoid, vitamins and anti-proliferative medications are preferably administered in hydrophobic media, namely ointment. However, ointments often form an impermeable barrier, so that metabolic products and excreta from the wounds to which they are applied are not easily removed or drained away. Furthermore, it is difficult for the active drug dissolved in the carrier to pass through the white petrolatum barrier layer into the wound tissue, so the efficacy of the drug is reduced. In addition, ointments and creams often do not create an environment for promoting respiration of the wound tissue and it is not favorable to the normal respiration of the skin. An additional disadvantage of petroleum jelly-based products relates to the greasy feeling left following their topical application onto the skin, mucosal membranes and wounds. A further problem of non aqueous compositions is achieving formulations in which the active agent is stable.

Some active agents are known to be generally unstable or susceptible to isomerisation or to breakdown, resulting in loss of activity and the use of stabilizers, anti oxidants antimicrobials and buffers and the like in aqueous compositions to protect active or cosmetic agents is known. The problems of protecting active pharmaceutical and cosmetic agents in waterless environments, such as polar compositions are multifold and can vary according to the type of waterless environment and the nature of the agent being used. It has been surprisingly found that factors like small levels of acid residues in the raw materials can be significant in influencing agent stability. Similarly, the presence of low levels of metal ions can act to catalyze reactions or breakdown. Likewise, the presence of agents in a waterless environment that results in

ionization or leads to oxidation can act to cause reactions or breakdown. There is therefore a need for simple and elegant solutions to stabilize active ingredients in a waterless or substantially environment.

It would be particularly advantageous and there is an unmet need to have a waterless vehicle additive that is suitable for use not merely one type of API but is adaptable for use with one or more API's from a wide range of different types of API's with relatively minimal or minor adjustment.

Foams and, in particular, foam emulsions are complicated systems which do not form under all circumstances. Changes in foam emulsion composition, such as by the addition of active ingredients may destabilize the foam. There is, therefore, a need for a foam composition, which provides desirable properties to the skin and can remain stable whilst accommodating a variety of active ingredients.

Formulations based on oil or ointment, emollients have a number of useful attributes making them suitable candidates for topical pharmaceutical and cosmetic compositions including foamable compositions. They are inherently stable and inert which are clearly desirable characteristics. They are able to moisturize and soften the skin and in appropriate amounts can act as a protective or barrier layer and can form a barrier to water. By appropriate formulation they can act to improve drug delivery to the skin and yet remain resistant to being washed off. On the other hand they are by their nature greasy materials and can be difficult to formulate particularly into a topical foamable composition that can deliver substantially uniform and stable composition or foam that ameliorates or overcomes the look and feel of a greasy material, especially where that composition is waterless or substantially so. It is further a problem to incorporate into such a vehicle pharmaceutically effective amounts of one or more active pharmaceutical ingredients such that they are uniformly present throughout the formulation and are effectively delivered without the use of an alcohol in the formulation.

On one level it is far from simple or obvious to produce waterless foamable compositions that when released produce foams of quality suitable for pharmaceutical or cosmetic application. On a further level having realized a carrier that will produce a waterless foam of quality there is an additional difficulty to be overcome, namely how to adapt the formula and achieve a formulation, which can accept a range of various active pharmaceutical and cosmetic agents such that the composition and active agent are stable and the foam produced remains of quality. Specifically, one of the challenges in preparing such waterless or substantially waterless foamable compositions is ensuring that the active pharmaceutical or therapeutic agent does not react, isomerizes or otherwise break down to any significant extent during its storage and use. Particularly, there remains an unmet need for improved, easy to use, stable and non-irritating foam formulations, with unique therapeutic or beneficial properties containing a stable or stabilized active pharmaceutical or cosmetic agent.

There remains an unmet need for improved, easy to use, stable and non-irritating topical foam formulations containing a stable or stabilized active pharmaceutical or cosmetic agent having a therapeutic or beneficial effect, intended for treatment of dermal and mucosal tissues.

SUMMARY

The present invention relates to a waterless composition as a vehicle in which an active pharmaceutical or cosmetic agent, when added is stable or stabilized.

The present invention also relates to a foamable waterless composition as a vehicle in which an active pharmaceutical or

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cosmetic agent, when added is stable or stabilized by the presence of a modulating agent.

The present invention more particularly relates to modulating agents that are able to be effective in relatively low concentrations and which have little or no significant effect on the compositions and on the foam compositions of the present invention.

According to one or more embodiments there is provided a waterless composition as a vehicle in which a modulating agent is incorporated and which is capable of stabilizing an active pharmaceutical or cosmetic agent, when added.

According to one or more embodiments there is provided a waterless vehicle, an active agent that is susceptible, to one or more of reaction, breakdown, ionization or oxidation and a modulating agent. In an embodiment the waterless vehicle comprises a hydrophobic solvent. In another embodiment it comprises a hydrophilic solvent.

According to one or more embodiments, the carrier, includes: a waterless solvent, a stabilizing surfactant, and or a polymeric agent, and in which is incorporated a modulating agent.

According to one or more embodiments, the carrier is a foamable carrier, and includes: a waterless solvent, a stabilizing surfactant, and or a polymeric agent, and a propellant and in which is incorporated a modulating agent.

In an embodiment the carrier and modulating agent formulation is capable of stabilizing an active pharmaceutical or cosmetic agent in a substantially waterless environment.

According to one or more embodiments there is provided a waterless composition comprising

one or more active agents and a carrier for topical delivery of the one or more active agents suitable for stabilizing at least one of said one or more active agents, said carrier comprising a waterless solvent and an effective amount of a modulating agent;

wherein the at least one active agent is chemically unstable in the carrier in the absence of a modulating agent;

wherein the modulating agent is capable of and is selected to modulate or adjust the artificial pH of the carrier to an artificial pH or to provide an artificial pH buffering effect such that the chemical stability of the at least one active agent is increased as compared to its stability in the carrier without the modulating agent.

According to one or more embodiments of the present invention, pharmaceutical or cosmetic composition is foamable and, includes: a waterless solvent, a stabilizing surfactant, and or a polymeric agent, a modulating agent, a propellant and one or more active pharmaceutical or cosmetic agents.

According to one or more embodiments of the present invention, the active agent itself can have characteristics of a modifying agent.

According to one or more embodiments of the present invention, the carrier, includes:

a. a waterless solvent comprising about 25% to about 98% of at least polar solvent selected from the group consisting of (1) a polyol; and (2) a polyethylene glycol or combinations thereof;

b. a modulating agent;

c. a stabilizing agent selected from the group consisting of a surface-active agent; and about 0.01% to about 5% by weight of at least one polymeric agent or mixtures thereof;

wherein the carrier is shakable and wherein if the composition is stored in an aerosol container and comprises a liquefied or compressed gas propellant at a concentration of about 3%

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to about 25% by weight of the total composition it will upon release expand to form a breakable foam.

According to one or more embodiments the active agent is susceptible to reaction, breakdown, ionization, or oxidation.

According to one or more embodiments of the present invention, the foamable pharmaceutical composition, includes:

1. a waterless solvent comprising about 25% to about 98% of at least polar solvent selected from the group consisting of (1) a polyol; and (2) a polyethylene glycol or combinations thereof;

2. a modulating agent;

3. a stabilizing agent selected from the group consisting of a surface-active agent and about 0.01% to about 5% by weight of at least one polymeric agent;

4. a liquefied or compressed gas propellant at a concentration of about 3% to about 25% by weight of the total composition; and

5. an effective amount of an active pharmaceutical or cosmetic agent;

wherein the carrier is shakable and wherein the composition is stored in an aerosol container and upon release expands to form a breakable foam.

According to one or more embodiments there is provided a foamable waterless composition comprising:

a. a therapeutically effective concentration of one or more active agents;

b. a carrier for topical delivery of the one or more active agents suitable for stabilizing at least one of said one or more active agents, comprising

i. about 25% to about 98% of at least polar solvent selected from the group consisting of (1) a polyol; and (2) a polyethylene glycol;

ii. 0% to about 75% of a secondary polar solvent;

iii. an effective amount of a modulating agent

iv. a stabilizing agent selected from the group consisting of a surface-active agent; about 0.01% to about 5% by weight of at least one polymeric agent and mixtures thereof.

v. a liquefied or compressed gas propellant at a concentration of about 3% to about 25% by weight of the total composition

wherein the at least one active agent is chemically unstable in the carrier in the absence of a modulating agent;

wherein the modulating agent is capable of and is selected to modulate or adjust the artificial pH of the carrier to an artificial pH or to provide an artificial pH buffering effect such that the chemical stability of the at least one active agent is increased as compared to its stability in the carrier without the modulating agent.

wherein the carrier is shakable or flowable; and

wherein the composition is stored in an aerosol container and upon release expands to form a breakable foam.

The present invention further relates to said composition comprising one or more additional active agents.

The present invention further relates to said composition comprising one or more additional or secondary polar solvents.

In some embodiments, the foamable cosmetic or pharmaceutical composition is non-flammable, wherein said gas propellant contains hydrofluorocarbon.

According to one or more embodiments there is provided a method of treating a disorder of mammalian subject, comprising:

administering a composition to a target site, the composition comprising:

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one or more active agents and a carrier for topical delivery of the one or more active agents suitable for stabilizing at least one of said one or more active agents, said carrier comprising a waterless solvent and an effective amount of a modulating agent;

wherein the at least one active agent is chemically unstable in the carrier in the absence of a modulating agent; wherein the modulating agent is capable of and is selected to modulate or adjust the artificial pH of the carrier to an artificial pH or to provide an artificial pH buffering effect such that the chemical stability of the at least one active agent is increased as compared to its stability in the carrier without the modulating agent.

According to one or more embodiments there is also provided a method of treating a disorder of mammalian subject, comprising:

administering a foamable composition to a target site, the composition comprising:

a foamable waterless composition comprising:

a. a therapeutically effective concentration of one or more active agents;

b. a carrier for topical delivery of the one or more active agents suitable for stabilizing at least one of said one or more active agents, comprising

i. about 25% to about 98% of at least polar solvent selected from the group consisting of (1) a polyol; and (2) a polyethylene glycol;

ii. 0% to about 75% of a secondary polar solvent;

iii. an effective amount of a modulating agent

iv. a stabilizing agent selected from the group consisting of a surface-active agent; about 0.01% to about 5% by weight of at least one polymeric agent and mixtures thereof.

v. a liquefied or compressed gas propellant at a concentration of about 3% to about 25% by weight of the total composition

wherein the at least one active agent is chemically unstable in the carrier in the absence of a modulating agent;

wherein the modulating agent is capable of and is selected to modulate or adjust the artificial pH of the carrier to an artificial pH or to provide an artificial pH buffering effect such that the chemical stability of the at least one active agent is increased as compared to its stability in the carrier without the modulating agent.

wherein the carrier is shakable or flowable; and

wherein the composition is stored in an aerosol container and upon release expands to form a breakable foam.

According to one or more embodiments there is also provided foamable waterless composition comprising:

a. a therapeutically effective concentration of one or more active agents;

b. a carrier delivery of the one or more active agents suitable for stabilizing at least one of said one or more active agents, comprising

i. about 25% to about 98% of at least polar solvent selected from the group consisting of (1) a polyol; and (2) a polyethylene glycol;

ii. 0% to about 75% of a secondary polar solvent;

iii. an effective amount of an modulating agent

iv. a stabilizing agent selected from the group consisting of a surface-active agent; about 0.01% to about 5% by weight of at least one polymeric agent and mixtures thereof.

v. a liquefied or compressed gas propellant at a concentration of about 3% to about 25% by weight of the total composition

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wherein the at least one active agent is chemically unstable in the carrier in the absence of a modulating agent; wherein the modulating agent comprises an effective amount of one or more agents that are capable of impeding said destabilization and or are capable of stabilizing the active agent by chelating a metal ion such that the modulating agent is capable of reducing in the waterless carrier the availability of metal ions so the stability of at least one active agent is improved when compared to its stability in the carrier without the modulating agent;

wherein the carrier is shakable or flowable; and

wherein the composition is stored in an aerosol container and upon release expands to form a breakable foam.

According to one or more embodiments there is also provided a carrier where the modulating agent acts by impeding ionization and or by impeding oxidation.

According to one or more embodiments there is also provided a foamable waterless carrier for use with a therapeutically effective concentration of one or more active agents comprising:

(i) about 25% to about 98% of at least polar solvent selected from the group consisting of (1) a polyol; and (2) a polyethylene glycol; 0% to about 75% of a secondary polar solvent;

(ii) an effective amount of a modulating agent

(iii) a stabilizing agent selected from the group consisting of a surface-active agent; about 0.01% to about 5% by weight of at least one polymeric agent and mixtures thereof.

(iv) a liquefied or compressed gas propellant at a concentration of about 3% to about 25% by weight of the total composition

wherein at least one active agent if present is susceptible, to one or more of reaction, breakdown, ionization or oxidation;

wherein the modulating agent comprises an effective amount of one or more agents that are capable of impeding said destabilization and or are capable of stabilizing the active agent primarily by modulating or adjusting the artificial pH of the carrier such that the modulating agent is capable of producing in the waterless carrier an artificial pH or an artificial pH buffering effect at about a pH or pH range in which the stability of at least one active agent is improved when compared to its stability in the carrier without the modulating agent and or by chelating a metal ion such that the modulating agent is capable of reducing in the waterless carrier the availability of metal ions so the stability of at least one active agent is improved when compared to its stability in the carrier without the modulating agent;

wherein the carrier is shakable or flowable; and

wherein the composition is stored in an aerosol container and upon release expands to form a breakable foam.

The present invention further provides a method of treating, alleviating or preventing a disorder of mammalian subject, comprising administering a therapeutically effective amount of the above-mentioned compositions to an afflicted target site.

The present invention further provides use of a therapeutically effective amount of the above-mentioned compositions as a medicament or in the manufacture of a medicament.

The present invention further provides a therapeutically effective amount of the above-mentioned compositions for use as a medicament or in the manufacture of a medicament.

All % values are provided on a weight (w/w) basis.

DETAILED DESCRIPTION

In one or more embodiments there is provided a waterless composition for use as a vehicle in which an active pharmaceutical or cosmetic agent, when added is stable or stabilized. Active pharmaceutical and cosmetic agents are more generally referred to as a therapeutic agent.

In one or more embodiments there is provided a waterless composition as a vehicle in which a modulating agent is incorporated and which is capable of stabilizing an active pharmaceutical or cosmetic agent, when added.

In an embodiment the carrier and modulating agent formulation is capable of stabilizing an active pharmaceutical or cosmetic agent in a substantially waterless or non aqueous environment.

In an embodiment the carrier and modulating agent formulation is capable of stabilizing an active pharmaceutical or cosmetic agent in a substantially waterless environment, where the active agent has low or minimal susceptibility to water and can withstand up to about 10% water and more preferably up to about 5% water.

In one or more embodiments there is provided a waterless composition for use as a vehicle in which an active pharmaceutical or cosmetic agent, when added is stable or stabilized by the presence of a modulating agent.

In one or more embodiments there is provided a foamable waterless composition for use as a vehicle in which an active pharmaceutical or cosmetic agent, when added is stable or stabilized by the presence of a modulating agent.

According to one or more embodiments, it is possible to make excellent lotions, creams, ointments and foams from waterless compositions. Such compositions containing a modulating agent as described herein are ideal carriers for active pharmaceutical ingredients that are soluble in polar solvents and which may be potentially unstable in an aqueous environment, for example, following a change in pH, or the introduction a metal catalyst or in the presence of an ionization or oxidation agent.

It has been found that differences in the level and type of residues in cosmetic and pharmaceutical grade materials and agents can significantly and seriously influence the stability of an active pharmaceutical or cosmetic agent. Whilst it might be expected that active agents would be more stable in pure raw materials with practically no residues it was surprisingly observed that small levels of residues in raw materials were actually helpful in improving the stability of and stabilizing active ingredients in certain waterless compositions. On the other hand active ingredients were unstable in certain other waterless compositions.

In the waterless polar environments the concepts of pH, pK, and the like are artificial and may only give approximate guidance. It has been surprisingly found that in a non-classical waterless polar environment of foamable carriers, compositions and foam's that active ingredients can be susceptible to break down, isomerization, oxidation or reaction in the presence of acid or basic residues, which in small quantities are able in a non classical way to take the active agent outside its preferred environmental window and facilitate instability. Likewise such breakdown etc. could be catalyzed by the presence of metal ions in the waterless polar environment. Following investigation it has been discovered that the introduction of an acid or base or buffer in a non classical

non-aqueous polar environment of foamable carriers, compositions and foam's can act to prevent or impede such breakdown etc. Similarly, the introduction of a chelating agent can also act to prevent or impede catalyzation of such breakdown etc. Likewise, introduction of an anti ionization or antioxidant agent may also act to prevent or impede such reaction etc.

It has been surprisingly discovered that one can modulate the environment of a non-aqueous foamable, carrier, composition or foam to provide a stable environmental window for the active agent in the non-aqueous environment. The modifying or modulating affect of the modulating agent on the waterless environment prevents or minimizes a so-called 'change in the artificial pH range' and/or locks up available metal ions which could otherwise act as a catalyst in the waterless environment and/or impedes ionization or oxidation of the active agent.

Following investigation, modulating agents are identified, which by their presence are able to stabilize active pharmaceutical or cosmetic agents in a waterless or substantially waterless environment. More particularly, they can be effective at relatively low concentrations that have little or no significant effect on the foam compositions of the present invention.

According to one or more embodiments there is provided a waterless composition as a vehicle in which a modulating agent is incorporated and which is capable of stabilizing an active pharmaceutical or cosmetic agent, when added.

According to one or more embodiments there is provided a waterless vehicle, an active agent that is susceptible, to one or more of reaction, breakdown, ionization or oxidation and a modulating agent. In an embodiment the waterless vehicle comprises a hydrophobic solvent. In another embodiment it comprises a hydrophilic solvent.

According to one or more embodiments, the carrier, includes: a waterless solvent, a stabilizing surfactant, and or a polymeric agent, and in which is incorporated a modulating agent.

According to one or more embodiments, the carrier is a foamable carrier, and includes: a waterless solvent, a stabilizing surfactant, and or a polymeric agent, and a propellant and in which is incorporated a modulating agent.

According to one or more preferred embodiments, the carrier comprises a stabilizing agent comprising a surfactant and a polymeric agent. This is particularly helpful for foamable compositions where the combination can be synergistic or complimentary in providing a robust stable foam of quality with a reasonable collapse time.

In an embodiment the carrier and modulating agent formulation is capable of stabilizing an active pharmaceutical or cosmetic agent in a substantially waterless environment.

According to one or more embodiments, pharmaceutical or cosmetic composition is foamable and, includes: a waterless solvent, a stabilizing surfactant, and or a polymeric agent, a modulating agent, a propellant and one or more active pharmaceutical or cosmetic agents.

According to one or more embodiments, the active agent itself can have characteristics of a modifying agent.

According to one or more embodiments, the carrier, includes:

- (a) a waterless solvent comprising about 25% to about 98% of at least polar solvent selected from the group consisting of (1) a polyol; and (2) a polyethylene glycol or combinations thereof;
- (b) a modulating agent;

(c) a stabilizing agent selected from the group consisting of a surface-active agent and about 0.01% to about 5% by weight of at least one polymeric agent and mixtures thereof;

wherein the carrier is shakable or flowable and wherein if the composition is stored in an aerosol container and further comprises a liquefied or compressed gas propellant at a concentration of about 3% to about 25% by weight of the total composition it will upon release expand to form a breakable foam.

According to one or more embodiments the active agent is susceptible to reaction, breakdown, ionization, or oxidation.

According to one or more embodiments, the active agent itself can have characteristics of a modifying agent.

According to one or more embodiments, the foamable carrier, includes:

1. a waterless solvent comprising about 25% to about 98% of at least polar solvent selected from the group consisting of (1) a polyol; and (2) a polyethylene glycol or combinations thereof;
2. a modulating agent;
3. a stabilizing agent selected from the group consisting of a surface-active agent; and about 0.01% to about 5% by weight of at least one polymeric agent and mixtures thereof; and
4. a liquefied or compressed gas propellant at a concentration of about 3% to about 25% by weight of the total composition;

wherein the composition is shakable or flowable; and wherein the composition is stored in an aerosol container and upon release expands to form a breakable foam.

According to one or more embodiments, the foamable pharmaceutical composition, includes:

1. a waterless solvent comprising about 25% to about 98% of at least polar solvent selected from the group consisting of (1) a polyol; and (2) a polyethylene glycol or combinations thereof;
2. a modulating agent;
3. a surface-active agent;
4. about 0.01% to about 5% by weight of at least one polymeric agent;
5. a liquefied or compressed gas propellant at a concentration of about 3% to about 25% by weight of the total composition; and
6. an effective amount of an active pharmaceutical or cosmetic agent;

wherein the carrier is shakable or flowable; and wherein the composition is stored in an aerosol container and upon release expands to form a breakable foam.

The problem of producing a pharmaceutical composition that can provide a stable or stabilized environment or he more formidable problem a foamable composition which can produce a breakable foam of quality and a stabilized environment so that the active pharmaceutical agent does not substantially break down over a reasonable time period sufficient for normal pharmaceutical or cosmetic use is surprisingly resolved by having both a polymeric agent and modulating agent present in the foamable composition.

In one or more embodiments the polymeric agent is selected from a bioadhesive agent, a gelling agent, a film forming agent and a phase change agent and can be from about 0.01% to about 5% by weight, preferably 0.2 to 3%.

In one or more embodiments the ratio of polymeric agent to surfactant is about 1:10 to about 10:1; about 1:5 to about 5:1; about 3:7 to about 7:3; and about 2:1 to about 1:2.

The provision and selection of polymeric agent is however not straightforward. The polymers should be miscible or swell in the waterless solvent. It has been found that in the case of modified cellulose that lower molecular weight cellulose polymer derivatives are preferable.

In one or more preferred embodiments the polymeric agent is hydroxypropyl cellulose.

In another preferred embodiments the polymeric agent is or Carbomer such as Carbopol 934®.

According to one or more embodiments, the pre-foamable carrier; the pre-foamable pharmaceutical or cosmetic composition; the foamable carrier, or the foamable pharmaceutical or cosmetic composition further includes 0.1% to about 75% of a secondary polar solvent.

In one or more embodiments there is provided a vehicle additive, preferably a foamable vehicle additive that is suitable for use with not merely one type of active pharmaceutical ingredient ("API") but is adaptable for use with one or more API's from a wide range of different types of API's with appropriate and usually relatively minimal or minor adjustment. For example, by altering the amount of a component or by the addition or replacement of a buffer, stabilizer, anti ionization agent or an antioxidant as would be appreciated by a person skilled in the art with the benefit of the teachings herein. In one or more other embodiments there is provided one or more pharmaceutical or cosmetic base compositions that are suitable for use with modulating agents.

In one or more embodiments there is provided a vehicle additive, preferably a foamable one that is suitable for use as a vehicle base for delivery for API's, which are by their nature unstable or reactive or isomerizes or oxidize.

In a further embodiment the modulating agent is preferably between about 0.05% to about 5% by weight of the composition.

In a further embodiment the surfactant and polymeric agent and their amounts are selected so that the composition is sufficiently shakable or in certain limited cases so that it is flowable albeit not shakable so that extrusion and substantially uniform composition formation, particularly foam extrusion and formation is not hampered. To this extent, the maximum effective amount of surfactant and polymeric agent that may be used may be limited by the need for shakability and as a minimum by the need for flowability.

In a further embodiment of the present invention the propellant is preferably between about 5% to about 12% by weight of the composition.

In one or more embodiments of the pharmaceutical or cosmetic foamable product is non-flammable.

By waterless is meant that the composition contains no or substantially no, free or unassociated or absorbed water. It will be understood by a person of the art that the waterless solvents and substances miscible with them of the present invention can be hydrophilic and can contain water in an associated or unfree or absorbed form and may absorb water from the atmosphere and the ability to do so is its hygroscopic water capacity.

In one or more embodiments the carrier comprises an active pharmaceutical or cosmetic agent, which degrades in the presence of water, and in such cases the present of water in the composition is clearly not desirable. Thus, in certain preferred embodiments, the composition is waterless. In other embodiments the active agent may tolerate the presence of a small amount of water and the waterless composition is substantially non-aqueous. The term "substantially non-aqueous" is intended to indicate that the waterless composition has water content below about 5%, preferably below about 2%, such as below about 1.5%.

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In one or more embodiments the active agent has low or minimal sensitivity and can tolerate water to about 10% or less.

Upon release from an aerosol container, the foamable carrier forms an expanded foam suitable for the treatment of an infected surface and for topical administration to the skin, a body surface, a body cavity or a mucosal surface.

Waterless Solvent

In one or more embodiments of the present invention the waterless solvent comprises about 25% to about 98% of at least a polar solvent selected from the group consisting of (1) a polyol; and (2) a polyethylene glycol or combinations thereof.

In one or more embodiments of the present invention the waterless solvent comprises about 0.1% to about 75% of a secondary polar solvent.

Polar Solvent

The identification of a "polar solvent", as used herein, is not intended to characterize the solubilization capabilities of the solvent for any specific active agent or any other component of the foamable composition. Rather, such information is provided to aid in the identification of materials suitable for use as a part in the foamable compositions described herein.

Polyol
In an embodiment of the present invention, the polar solvent is a polyol. A polyol is an organic substance that contains at least two hydroxy groups in its molecular structure.

In one or more embodiments, the foamable carrier contains at least one diol (a compound that contains two hydroxy groups in its molecular structure). Examples of diols include propylene glycol (e.g., 1,2-propylene glycol and 1,3-propylene glycol), butanediol (e.g., 1,2-butanediol, 1,3-butanediol, 2,3-butanediol and 1,4-butanediol), pentanediol (e.g., 1,3-pentanediol and 1,4-pentanediol), butanediol, pentanediol (e.g., pentane-1,2-diol, pentane-1,3-diol, pentane-1,4-diol, pentane-1,5-diol, pentane-2,3-diol and pentane-2,4-diol), hexanediol (e.g., hexane-1,6-diol, hexane-2,3-diol and hexane-2,5,6-diol), octanediol (e.g., 1,8-octanediol), neopentyl glycol, 2-methyl-1,3-propanediol, diethylene glycol, triethylene glycol, tetraethylene glycol, dipropylene glycol and dibutylene glycol.

In one or more embodiments, the foamable carrier contains at least one triol (a compound that contains three hydroxy groups in its molecular structure), such as glycerin, butane-1,2,3-triol, butane-1,2,4-triol and hexane-1,2,6-triol.

In one or more embodiments, the polyol is a mixture of polyols. In one or more embodiments, the mixture of polyols contains at least one diol and at least one triol. According to certain embodiments the ratio between the diol and triol is between 9:1 and 1:1.

In one or more embodiments, part of mixture of polyols is a saccharide. Exemplary saccharides include, but are not limited to monosaccharide, disaccharides, oligosaccharides and sugar alcohols.

A monosaccharide is a simple sugar that cannot be hydrolyzed to smaller units. Empirical formula is $(CH_2O)_n$ and range in size from trioses ($n=3$) to heptoses ($n=7$). Exemplary monosaccharide compounds are ribose, glucose, fructose and galactose.

Disaccharides are made up of two monosaccharides joined together, such as sucrose, maltose and lactose.

A sugar alcohol (also known as a polyol, polyhydric alcohol, or polyalcohol) is a hydrogenated form of saccharide, whose carbonyl group (aldehyde or ketone, reducing sugar) has been reduced to a primary or secondary hydroxyl group. They are commonly used for replacing sucrose in foodstuffs, often in combination with high intensity artificial sweeteners

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to counter the low sweetness. Some exemplary sugar alcohols, which are suitable for use according to the present invention are mannitol, sorbitol, xylitol, maltitol, lactitol. (Maltitol and lactitol are not completely hydrogenated compounds—they are a monosaccharide combined with a polyhydric alcohol). Mixtures of polyols, including (1) at least one polyol selected from a diol and a triol; and (2) a saccharide are contemplated within the scope of the present invention.

Polyethylene Glycol

In an embodiment of the present invention, the polar solvent consists of a polymerized ethylene glycol, namely polyethylene glycol, which is also termed "PEG". Exemplary PEGs are provided in the following table.

Composition	Av. Molecular weight	Appearance	Melting point (° C.)
PEG 200	190~210	Oily liquid	
PEG 300	285~315	Oily liquid	
PEG 400	380~420	Oily liquid	
PEG 600	570~630	Oily liquid	17~22
PEG 1000	950~1050	Solid	35~40
PEG 4000	3800~4400	Solid	53~58
PEG 6000	5600~6400	Solid	55~60
PEG 8000	7500~8500	Solid	58~65

Thus, in an embodiment of the present invention, the PEG is selected from the group consisting of PEG 200, PEG 300, PEG 400, PEG 600, PEG 1000, PEG 4000, PEG 6000 and PEG 8000. The foamable carrier according to the present invention can contain a single PEG or a mixture of two or more PEGs. PEGs having molecular weight of more than about 1000 possess gelling properties; i.e., they increase the viscosity of a composition. Therefore, by combining PEGs with different molecular weights/melting points, one can attain varying levels of flowability as desirable for the treatment of a given target site. The concentration of the PEG should be in a level that results in viscosity, prior to filling of the composition into aerosol canisters, of less than 12,000 CPs, and more preferably, less than 10,000 CPs.

Secondary Polar Solvent

Optionally, a secondary polar solvent is added to the foamable composition of the present invention. The secondary polar solvent is selected from a variety of organic solvents that are typically miscible on both water and oil. Examples of polar solvent that can be contained in the foamable carrier of the present invention include dimethyl isosorbide, tetrahydrofurfuryl alcohol polyethyleneglycol ether (glycofuro), DMSO, pyrrolidones, (such as N-Methyl-2-pyrrolidone and 1-Methyl-2-pyrrolidinone), ethyl proxitol, dimethylacetamide (DMAc), PEG-type surfactants and alpha hydroxy acids, such as lactic acid and glycolic acid.

Appropriate use of a secondary solvent in a waterless foam composition can help improve delivery of active agents to a target area. Foam compositions of the present invention, for which the solvent includes a secondary solvent, can increase the levels of the active agent in the waterless composition and thus, provide high delivery and improved therapy.

Solubilization and Penetration Enhancement

In many cases, polyols, PEGs and polar solvents possess a high solubilizing power and thus, they can enable increased concentrations of a pharmaceutical active agent. Polyols, PEGs and polar solvents are also known for their skin penetration enhancement properties. These properties enable high drug bioavailability in the target area of treatment, resulting in an enhanced therapeutic effect. Occasionally,

combinations of a polyol, PEGs and a secondary polar solvent, exhibit an increased permeability across the skin, as suggested, for example, in Eur J Pharm Biopharm. 1998 November; 46(3):265-71.

Thus, in one or more embodiments, the foamable carrier contains (1) at least one polar solvent, selected from a polyol (selected from a diol and a triol) and PEG; and (2) at least one secondary polar solvent.

In one or more embodiments, the foamable carrier contains (1) a mixture of at least two polyols; and (2) at least one secondary polar solvent. In additional embodiments, the foamable carrier contains a mixture of at least one polyol and at least one PEG; yet in other embodiments the foamable carrier contains (1) a mixture of at least one polyol and at least one PEG and (2) at least one secondary polar solvent.

According to certain embodiments the ratio between the polyol and/or PEG and the secondary polar solvent is between 9:1 and 1:1.

In certain embodiments, the polyol is selected from the group consisting of propylene glycol, hexylene glycol and glycerin (and mixtures thereof); and the secondary polar solvent is selected from the group consisting of dimethyl isosorbide, diethylene glycol monoethyl ether, a liquid polyethylene glycol and glycofurol.

In certain embodiments, the foamable carrier contains (1) at least one polyol; and (2) dimethyl isosorbide.

Short chain alcohols, such as ethanol and propanol are known as polar solvents, however, according to one or more embodiments, the composition of the present invention is substantially alcohol-free, i.e., free of short chain alcohols. Short chain alcohols, having up to 5 carbon atoms in their carbon chain skeleton and one hydroxyl group, such as ethanol, propanol, isopropanol, butanol, iso-butanol, t-butanol and pentanol, are considered less desirable polar solvents due to their skin-irritating effect.

Thus, in certain embodiments, the composition is substantially alcohol-free and includes less than about 5% final concentration of lower alcohols, preferably less than about 2%, more preferably less than about 1%. However, in other embodiments, a short chain alcohol can be included in the composition, as long as the ratio between the short chain alcohol and the polyol is less than 1:4 by weight.

Modulating Agent

The term modulating agent is used to describe an agent which can improve the stability of or stabilize a carrier or a foamable composition and or an active agent by modulating the effect of a substance or residue present in the carrier or composition. The substance or residue may for example be acidic or basic and potentially alter an artificial pH in a waterless or substantially non aqueous environment or it may be one or more metal ions which may act as a potential catalyst in a waterless or substantially non aqueous environment or it may be an ionisation agent or it may be an oxidizing agent.

In one or more other embodiments the modulating agent is used in a waterless composition. In one or more embodiments the modulating agent is used in a substantially non aqueous composition

In one or more embodiments the modulating agent is used to describe an agent which can affect pH in an aqueous solution.

The agent can be any of the known buffering systems used in pharmaceutical or cosmetic formulations as would be appreciated by a man of the art. It can also be an organic acid, a carboxylic acid, a fatty acid an amino acid, an aromatic acid, an alpha or beta hydroxyl acid an organic base or a nitrogen containing compound.

In one or more further embodiments the modulating agent is used to describe an agent, which is a chelating or sequestering or complexing agent that is sufficiently soluble or functional in the waterless solvent to enable it to "mop up" or "lock" metal ions.

In the embodiment modulating agent is used to describe an agent which can effect pH in an aqueous solution the term modulating agent more particularly means an acid or base or buffer system or combinations thereof, which is introduced into or is present in and acts to modulate the ionic or polar characteristics and any acidity or basicity balance of a waterless or substantially non aqueous carrier, composition, foamable carrier or foamable composition or resultant foam of the present invention.

The substance or residue can be introduced into the formulation from any one or more of the ingredients, some of which themselves may have acidic or basic properties. For example the polymer or solvent may contain basic residues in which case it may be desirable or beneficial to add an acid. Alternatively the surfactant may contain some acid residues in which case the addition of a base may be desirable and beneficial. In some cases more than one ingredient may contain residues which may ameliorate or compound their significance. For example if one ingredient provided weak acid residues and another stronger acid residues the artificial pH in a waterless environment should be lower. In contrast, if one residue was acid and the other basic the net effect in the formulation maybe significantly reduced. In some circumstances the active ingredient may favor an acidic pH or more significantly may need to be maintained at a certain acidic pH otherwise it may readily isomerize, chemically react or breakdown, in which case introducing acidic components might be of help. Likewise in some circumstances the active ingredient may favor a basic pH or more significantly may need to be maintained at a certain basic pH otherwise it may readily hydrolyse, undergo rearrangement, isomerize, chemically react or breakdown, in which case introducing basic components might be of help. In an embodiment of the present invention sufficient modulating agent is added to achieve an artificial pH in which the active agent is preferably stable. Such artificial pH may be acidic, maybe basic or may be neutral.

The terms pH, pKa, and pKb, buffers and the like are used in classical measurements of an aqueous solution. Such measurements are artificial in a waterless environment. Nevertheless, reference to and description below of such terms are made for convenience and clarity, since such terms are well defined and understood with reference to aqueous solutions and further due to the lack of an appropriate uniform way of describing and identifying the artificial or virtual pH, pK etc in a waterless environment in relation to the present invention. Although predictions of artificial pH can be made using dilution techniques of measurements of waterless formulations diluted in water they are formulation sensitive and specific and have to be carefully calibrated with complex formulas.

Waterless medium can be polar and protic yet it does not conform to classical ionic behavior.

A buffer, as defined by Van Slyke [Van Slyke, J. Biol. Chem. 52, 525 (1922)], is "a substance which by its presence in solution increases the amount of acid or alkali that must be added to cause unit change in pH".

A buffer solution is a solution of a definite pH made up in such a way that this pH alters only gradually with the addition of alkali or acid. Such a solution consists of a solution of a salt of the weak acid in the presence of the three acid itself. The pH of the solution is determined by the dissociation equilibrium of the free acid.

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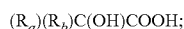
An acid can be a strong acid or a weak acid. A strong acid is an acid, which is a virtually 100% ionized in solution. In contrast, a weak acid is one which does not ionize fully when it is dissolved in water. The lower the value for pKa, the stronger is the acid and likewise, the higher the value for pKa the weaker is the acid.

A base can be a strong base or a weak base. A strong base is something, which is fully ionic with 100% hydroxide ions. In contrast, a weak base is one which does not convert fully into hydroxide ions in solution. The lower the value for pKb, the stronger is the base and likewise, the higher the value for pKb the weaker is the base.

In general terms, three factors, which influence the strength of a base, are firstly the ease with which the lone pair takes up a hydrogen ion; secondly, the stability of ions being formed and thirdly, the way they interact with water such that if they pick up hydrogen ion's more readily it is a stronger base.

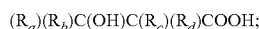
An acid in an amount to affect the composition's pH selected from the group consisting of:

(a) An alpha hydroxyl acid of formula I:



or a pharmaceutically acceptable salt, lactone, or solvate thereof, wherein R_a and R_b are independently selected from the group consisting of H, F, C, Br, and saturated or unsaturated, isomeric or non-isomeric, straight, branched, or cyclic C_1 - C_{25} alkyl, aralkyl, or aryl groups, wherein each of R_a and R_b may be optionally substituted with an OH, SH, CHO, COOH group;

(b) An aliphatic beta hydroxyacid of formula II:



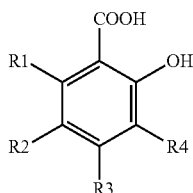
or a pharmaceutically acceptable salt, lactone, or solvate thereof, wherein R_a , R_b , R_c and R_d are independently selected from the group consisting of H, F, C, Br, and saturated or unsaturated, isomeric or non-isomeric, straight, branched, or cyclic C_1 - C_{25} alkyl, aralkyl, or aryl groups, wherein each of R_a and R_b may be optionally substituted with an OH, SH, CHO, COOH group.

Exemplary alpha hydroxyl acids and beta hydroxyl acids include, but are not limited to alpha-hydroxybutyric acid, alpha-hydroxyisobutyric acid, alpha-hydroxyisocaproic acid, alpha-hydroxyisovaleric acid, atrolactic acid, beta-hydroxybutyric acid, beta-phenyl lactic acid, beta-phenylpyruvic acid, citric acid, pyruvic acid, galacturonic acid, glucoheptonic acid, glucoheptono 1,4-lactone, gluconic acid, gluconolactone, glucuronic acid, glucuronolactone, glycolic acid, lactic acid, mandelic acid, mucic acid, pyruvic acid, saccharic acid, saccharic acid 1,4-lactone, tartaric acid and tartronic acid, 3-Hydroxybutanoic acid, quinic acid, isocitric acid, tropic acid, trethocanic acid, chlorolactic acid, citramalic acid, agaricic acid, aleuritic acid, pantoic acid, lactobionic acid, piscidic acid, hexulosonic acid or the anhydride thereof.

(c) An aromatic acid.

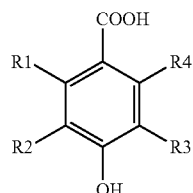
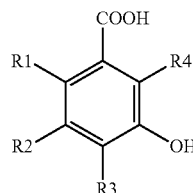
Exemplary aromatic acids include, but are not limited to benzoic acid, toluic acid, dimethyl benzoic acid, phthalic acid and nicotinic acid (heterocyclic).

(d) an aromatic hydroxyl acid of formula IIIa, IIIb and IIIc:



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-continued



The aromatic ring can contain solely carbon atoms or a combination of carbon atoms and other atoms (heterocyclic), wherein R_1 , R_2 , R_3 and R_4 are independently selected from the group consisting of H, F, C, Br, and saturated or unsaturated, isomeric or non-isomeric, straight, branched, or cyclic C_1 - C_{25} alkyl, aralkyl, or aryl groups.

Formula IIIa, wherein R is H, is identified as salicylic acid, yet another example of an aromatic hydroxyl acid is acetyl-salicylic acid.

(e) an alpha ketoacid of formula IV:



or a pharmaceutically acceptable salt, ester, or solvate thereof, wherein R_a and R_b are independently selected from the group consisting of H and saturated or unsaturated, isomeric or non-isomeric, straight, branched, or cyclic C_1 - C_{25} alkyl, aralkyl, or aryl groups, wherein R_a may be optionally substituted with an F, C, Br, I, OH, CHO, COOH, or alkoxy group having 1 to 9 carbon atoms;

(f) An aliphatic carboxylic acid.

Short chain carboxylic acids include formic acid, acetic acid and propionic acid.

A fatty acid is a carboxylic acid often with a long unbranched aliphatic tail (chain), which is either saturated or unsaturated. Carboxylic acids as short as butyric acid (4 carbon atoms) are considered to be fatty acids, while fatty acids derived from natural fats and oils may be assumed to have at least 8 carbon atoms, as exemplified in the following list:

Butyric (butanoic acid): $CH_3(CH_2)_2COOH$

Caproic (hexanoic acid): $CH_3(CH_2)_4COOH$

Caprylic (octanoic acid): $CH_3(CH_2)_6COOH$

Nonanoic acid: $CH_3(CH_2)_7COOH$

Capric (decanoic acid): $CH_3(CH_2)_8COOH$

Lauric (dodecanoic acid): $CH_3(CH_2)_{10}COOH$

Myristic (tetradecanoic acid): $CH_3(CH_2)_{12}COOH$

Palmitic (hexadecanoic acid): $CH_3(CH_2)_{14}COOH$

Stearic (octadecanoic acid): $CH_3(CH_2)_{16}COOH$

Arachidic (eicosanoic acid): $CH_3(CH_2)_{18}COOH$

Behenic (docosanoic acid): $CH_3(CH_2)_{20}COOH$

Octacosanoic: $CH_3(CH_2)_{26}COOH$

Optionally, the carbon atom chain of the fatty acid may have at least one double bond, as exemplifies in the following list:

Oleic acid: $CH_3(CH_2)_7CH=CH(CH_2)_7COOH$

Linoleic acid: $CH_3(CH_2)_4CH=CHCH_2CH=CH(CH_2)_7COOH$

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Alpha-linolenic acid: $\text{CH}_3\text{CH}_2\text{CH}=\text{CHCH}_2\text{CH}=\text{CHCH}_2\text{CH}=\text{CH}(\text{CH}_2)_7\text{COOH}$

Arachidonic acid

$\text{CH}_3(\text{CH}_2)_4\text{CH}=\text{CHCH}_2\text{CH}=\text{CHCH}_2\text{CH}=\text{CHCH}_2\text{CH}=\text{CH}(\text{CH}_2)_3\text{COOH}$

Eicosapentaenoic acid

Docosahexaenoic acid

Erucic acid: $\text{CH}_3(\text{CH}_2)_7\text{CH}=\text{CH}(\text{CH}_2)_{11}\text{COOH}$

Alpha-linolenic, docosahexaenoic, and eicosapentaenoic acids are examples of omega-3 fatty acids. Linoleic acid and arachidonic acid are omega-6 fatty acids. Oleic and erucic acid are omega-9 fatty acids.

A further class of carboxylic acids according to the present invention comprises a carboxylic acid, wherein the carbon atom chain is branched, such as valproic acid. The carbon chain of the fatty acid or fatty alcohol can be substituted with a hydroxyl group, such as 12-hydroxy stearic acid.

Short chain carboxylic acids such as formic acid and acetic acid are reasonably strong acids (pKa 3.77 and 4.76, respectively). Longer chain fatty acids have higher pKa values. Nonanoic acid, for example, has a pKa of 4.96.

(g) a dicarboxylic acid

In the context of the present invention, a dicarboxylic acid is an organic compound, having two carboxylic acid moieties on its carbon atom skeleton. They have the general molecular formula $\text{HOOC}-(\text{CH}_2)_n-\text{COOH}$.

In an embodiment of the present invention, the dicarboxylic acid is a short-chain dicarboxylic acid. The simplest short-chain dicarboxylic acid are oxalic acid (n=0), malonic acid (n=1), succinic acid (n=2) and glutaric acid (n=3).

Additional members of dicarboxylic acid group are derived from natural products or from synthesis, having "n" value from 4 up to 21. In one or more embodiments of the present invention, the dicarboxylic acid is selected from the group consisting of adipic acid (hexanedioic acid; n=4), pimelic acid (heptanedioic acid; n=5), suberic acid (octanedioic acid; n=6), azelaic acid (nonanedioic acid; n=7), sebacic acid (decanedioic acid; n=8) and dodecanedioic acid (n=10).

In an additional embodiment, the dicarboxylic acid contains 10 to 32 carbon atoms in their carbon atom skeleton, such as brassylic acid (n=11), thapsic acid (n=14), 14-methylnonacosanedioic acid (C29) and 14,15-dimethyltriacontanedioic acid (C30).

The carbon atom skeleton of the dicarboxylic acid can be saturated or unsaturated, such as in the case of undecylenic acid, maleic acid and fumaric acid.

In an additional embodiment, the dicarboxylic acid is branched, i.e., the carbon atom skeleton of the dicarboxylic acid can be substituted with at least one group selected from the group consisting of R, F, C, Br, OH, OR, SH, CHO, COOH, and NR_aR_b , wherein R, R_a and R_b are independently selected from the group consisting of H, saturated or unsaturated, isomeric or non-isomeric, straight, branched, or cyclic $\text{C}_1\text{-C}_{25}$ alkyl, aralkyl, or aryl groups. Exemplary branched dicarboxylic acids include aspartic acid, alpha-ketoglutaric acid, adipic acid 2-amino, aconitic acid, benzene dicarboxylic acid, citramalic acid, citric acid, cystathionine, glucuronic acid, glutamic acid, itaconic acid, malic acid, mucic acid, oxalacetic acid, diamino pimelic acid, saccharic acid, dimethyl succinic acid, tartaric acid, tartronic acid,

(h) Miscellaneous organic acids

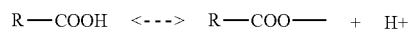
In an embodiment of the present invention, the organic acid is selected from the group consisting of ascorbic acid, isoascorbic acid, ethanesulfonic acid, glycerophosphoric acid, acetohydroxamic acid, aconitic acid, alpha-ketocaproic acid, aminomalonic acid, hippuric acid, hydrochloric acid, methanesulfonic acid, oxalic acid, phosphoric acid, sorbic

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acid, iminodiacetic acid, carnitine, nicotinic acid and retinoids, such as retinoic acid and isotretinoin.

(i) Amino acid

The a-COOH and a-NH₂ groups in amino acids are capable of ionizing (as are the acidic and basic R-groups of the amino acids). As a result of their ionizability the following ionic equilibrium reactions may be written:



The equilibrium reactions, as written, demonstrate that amino acids contain at least two weakly acidic groups. However, typically the carboxyl group is a far stronger acid than the amino group. At physiological pH (around 7.4) the carboxyl group will be unprotonated and the amino group will be protonated. An amino acid with no ionizable R-group would be electrically neutral at this pH. This species is termed a zwitterion.

Like typical organic acids, the acidic strength of the carboxyl, amino and ionizable R-groups in amino acids can be defined by the association constant, Ka or more commonly the negative logarithm of Ka, the pKa. The net charge (the algebraic sum of all the charged groups present) of any amino acid, peptide or protein, will depend upon the pH of the surrounding aqueous environment. As the pH of a solution of an amino acid or protein changes so too does the net charge. This phenomenon can be observed during the titration of any amino acid or protein. When the net charge of an amino acid or protein is zero the pH will be equivalent to the isoelectric point: pI.

The following table lists amino acids and their pKa's:

Acid	pK ₁ (COOH)	pK ₂ (NH ₂)	pK R Group
Glycine	2.4	9.8	
Alanine	2.4	9.9	
Valine	2.2	9.7	
Leucine	2.3	9.7	
Isoleucine	2.3	9.8	
Serine	2.2	9.2	~13
Threonine	2.1	9.1	~13
Cysteine	1.9	10.8	8.3
Methionine	2.1	9.3	
Aspartic Acid	2.0	9.9	3.9
Asparagine	2.1	8.8	
Glutamic Acid	2.1	9.5	4.1
Glutamine	2.2	9.1	
Arginine	1.8	9.0	12.5
Lysine	2.2	9.2	10.8
Histidine	1.8	9.2	6.0
Phenylalanine	2.2	9.2	
Tyrosine	2.2	9.1	10.1
Tryptophan	2.4	9.4	
Proline	2.0	10.6	

In addition, nonprotein amino acids are also suitable in accordance to the present invention, including but not limited to: B-alanine(3-alanine), 4-aminobutyrate (GABA), 3-cyanoalanine (B-cyanoalanine), 2-aminobutyric acid, 2-methylene-4-aminobutyric acid, 3-methylene-4-aminobutyric acid, 2-aminoisobutyric acid, 5-aminolevulinic acid, 2-amino-4-methylhexanoic acid (homoisoleucine), 2-amino-4-methylhex-4-enoic acid, 2-amino-4-methylhex-5-ynoic acid, 2-amino-3-methylpentanoic acid, 2-aminoadipic acid, 4-ethylideneglutamic acid, 3-aminoglutaric acid, 2-ami-

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nopimelic acid, N4-ethylasparagine, N4-methylasparagine, erythro-4-methylglutamic acid, 4-methyleneglutamic acid, 4-methyleneglutamine, N5-methylglutamine, N5-ethylglutamine (theanine), N5-isopropylglutamine, 2-amino-4-(aminooxy)butyric acid (canaline), 2,4-diaminobutyrate, N4-acetyl-2,4-diaminobutyrate, N4-lactyl-2,4-diaminobutyrate, N4-oxalyl-2,4-diaminobutyrate, 2,3-diaminopropionic acid, N3-acetyl-2,3-diaminopropionic acid, N3-methyl-2,3-diaminopropionic acid, N3-oxalyl-2,3-diaminopropionic acid, N6-acetyllysine, N6-methyllysine, N6-trimethyllysine (laminine), ornithine (2,5-diaminopentanoic acid), saccharopine (N6-(2'-glutamyl)lysine, 2,6-diaminopimelic acid, N4-(2-hydroxyethyl)asparagine, erythro-3-hydroxyaspartic acid, 4-hydroxyarginine, 4-hydroxycitrulline, threo-4-hydroxyglutamic acid, 3,4-dihydroxyglutamic acid, 3-hydroxy-4-methylglutamic acid, 3-hydroxy-4-methyleneglutamic acid, 4-hydroxy-4-methylglutamic acid, 4-hydroxyglutamine, N5-(2-hydroxyethyl)glutamine, 5-hydroxynorleucine, threo-4-hydroxyhomoarginine, homoserine, O-acetylhomoserine, O-oxalylhomoserine, O-phosphohomoserine, 4-hydroxyisoleucine, 5-hydroxymethylhomocysteine, threo-3-hydroxyisoleucine, 5-hydroxyisoleucine, 2-hydroxylysine, 4-hydroxylysine, 5-hydroxylysine, N6-acetyl-5-hydroxylysine, N6-trimethyl-5-hydroxylysine, 4-hydroxyornithine, mimosine, 4-hydroxynorvaline, 5-hydroxynorvaline, 2-amino-4,5-dihydroxypentanoic acid, 2-amino-4-hydroxypimelic acid, 4-hydroxyvaline, O-acetylserine, O-phosphoserine, pipercolic acid, (piperidine-2-carboxylic acid), 3-hydroxypipercolic acid, trans-4-hydroxypipercolic acid, trans-5-hydroxypipercolic acid, 5-hydroxy-6-methylpipercolic acid, 4,5-dihydroxypipercolic acid, trans-3-hydroxyproline, trans-4-hydroxyproline, trans-4-hydroxymethylproline, azetidine-2-carboxylic acid, N-(3-amino-3-carboxypropyl)azetidine-2-carboxylic acid, 4,5-dehydropipercolic acid (baikiain), 3-amino-3-carboxypyrrolidone (cucurbitine), 2-(cyclopent-2'-enyl)glycine, 5-hydroxytryptophan, albizziine (2-amino-3-ureidopropionic acid), arginosuccinic acid, canavinosuccinic acid, citrulline, homoarginine, homocitrulline, indospicine, O-ureidohomoserine, 6-hydroxykynurenine, 3-(4-aminophenyl)alanine, 3-(3-aminomethylphenyl)alanine, 3-(3-carboxyphenyl)alanine, 3-carboxytyrosine, 3-(3-hydroxymethylphenyl)alanine, 3-(3-hydroxyphenyl)alanine, 3-(3,4-dihydroxyphenyl)alanine (L-DOPA), 2-(phenyl)glycine, 2-(3-carboxyphenyl)glycine, 2-(3-carboxy-4-hydroxyphenyl)glycine, 2-(3-hydroxyphenyl)glycine, 2-(3,5-dihydroxyphenyl)glycine, 4-aminopipercolic acid, guvacine, 2-amino-4-(isoxazolin-5-one)-2-yl)butyric acid, lathyrine, tetrahydrolathyrine and ornithine.

In an embodiment of the present invention the organic modulating agent is a dimer or oligomer of amino acids.

In an embodiment of the present invention the organic modulating agent is an organic base.

In an embodiment the organic base is a nitrogen-containing organic compound.

In an embodiment the nitrogen-containing organic modulating compound is selected from, primary, secondary, tertiary and quaternary amines. The organic primary amine may include alkylamines such as methylamine and ethylamine; ethanolamine such as monoethanolamine and monoisopropanolamines; diamines such as ethylenediamine and 1,2-diaminopropane. The organic secondary amines include dialkylamines such as dimethylamine and diethylamine, diethanolamine and diisopropanolamine; N-methylethanolamine and N-ethylethanolamine. The organic tertiary amines include trialkylamines such as triethylamine and triethy-

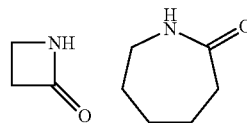
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lamine; triethanolamine; N-methyldiethanolamine and triisopropanolamine. The quaternary compounds preferably include basic choline.

In an embodiment the nitrogen-containing organic modulating compound is an amide. Amides are derivatives of oxoacids in which an acidic hydroxy group has been replaced by an amino or substituted amino group. Compounds having one, two, or three acyl groups on a given nitrogen are generically included and may be designated as primary, secondary and tertiary amides, respectively.

In an embodiment the nitrogen-containing organic modulating compound is an amine oxide. amine oxide are compounds derived from tertiary amines by the attachment of one oxygen atom to the nitrogen atom: $R_3N^+-O^-$.

In an embodiment the nitrogen-containing organic modulating compound is a lactam. Lactams are cyclic amides amino carboxylic acids, having a 1-azacycloalkan-2-one structure, or analogues having unsaturation or heteroatoms replacing one or more carbon atoms of the ring, as exemplified in the following structures:



Urea is another example of a nitrogen-containing modulating compound.

The modulating agent to the foamable composition of the present invention is useful for stabilizing pharmaceutical and cosmetic active agents which are unstable in certain pH conditions. It is known, for example, that active agents, which contain ester bond in their structure tend to undergo hydrolysis of the ester bond at basic pH levels. Therefore, the addition of an agent which avoids the formation of basic pH condition and thus, prevents degradation of such active agents. Many steroid compounds are known to undergo rearrangement at high pH, and again, adding an acidic modulating agent helps prevent such degradation. This is clearly exemplified by the stark difference in stability results for BMV in the absence and presence of a modulating agent as demonstrated in Examples 1 and 2 below. Another example of a pH-sensitive active agent is vitamin D, which degrades at low pH levels. In such a case, the addition of a basic modulating agent, such as triethanol amine is useful to maintain acceptable stability of this active agents as can be seen an exemplified in Example 5 below.

In certain cases, the stability of an active agent may be influenced by small quantities of, for example, metal ions in the waterless compositions. Such metal ions may act as a catalyst in facilitating the reaction or breakdown of the agent. Thus the modulating agent can be a chelating or sequestering or complexing agent on its own. In one or more embodiments of the present invention there is provided an effective amount of chelating agent which is sufficiently soluble or functional in the waterless solvent to enable it to "mop up" or "lock" metal ions.

For instance it is known that Polyphenols through the chelation of transition-metal ions, particularly those of iron and copper inhibit free radical formation and the propagation of free radical reactions (Brown et al. in Biochem. J 330, 1173-1178 (1998)). Citric acid, amino acids, and thylenediamine-tetraacetic acid also form chelates with metallic ions such as copper and iron, thus avoiding their catalytic action on the oxidation of lipids. Most of these chelating agents exhibit

little or no antioxidant activity when used alone, and therefore they are considered as synergistic agents of other antioxidants. Thus, they increase, to a great extent, the action of primary antioxidants.

In one or more embodiments of the present invention the chelating agent is selected from the group consisting of acetyl trihexyl citrate, aminotrimethylene phosphonic acid, beta-alanine diacetic acid, bismuth citrate, calcium disodium edta, citric acid, cyclohexanediamine tetraacetic acid, diammonium citrate, dibutyl oxalate, diethyl oxalate, diisobutyl oxalate, diisopropyl oxalate, dilithium oxalate, dimethyl oxalate, dipotassium edta, dipotassium oxalate, dipropyl oxalate, disodium edta, disodium edta-copper, disodium pyrophosphate, edta, etidronic acid, hedta, methyl cyclodextrin, oxalic acid, pentapotassium, triphosphate, pentasodium aminotrimethylene phosphonate, pentasodium pentetate, pentasodium triphosphate, pentetic acid, phytic acid, potassium citrate, sodium citrate, sodium dihydroxyethylglycinate, sodium gluceptate, sodium gluconate, sodium hexametaphosphate, sodium metaphosphate, sodium metasilicate, sodium oxalate, sodium trimetaphosphate, tea-edta, tetrahydroxypropyl ethylenediamine, tetrapotassium etidronate, tetrapotassium pyrophosphate, tetrasodium edta, tetrasodium etidronate, tetrasodium pyrophosphate, tripotassium edta, trisodium edta, trisodium hedta, trisodium nta, trisodium phosphate, malic acid, fumaric acid, maltol, succimer, penicillamine, dimercaprol, and desferrioxamine mesilate.]

Other authorized chelating agents are listed pursuant to annex 1, paragraph E.3.1 of regulation (EC) No 2003 (See Directive 67/548/EEC OJ 196, 16.8 1967, p1) and are also incorporated herein by reference.

In one or more preferred embodiments of the present invention the chelating agent is selected from the group consisting of ethylenediaminetetraacetic acid ("EDTA") and salts thereof such as disodium EDTA, tetrasodium EDTA and calcium disodium EDTA; diethylenetriaminepentaacetic acid ("DTPA") and salts thereof; hydroxyethylethylenediaminetriacetic acid ("HEDTA") and salts thereof and nitrilotriacetic acid ("NTA"); more preferably EDTA, HEDTA and their salts; most preferably EDTA and its salts.

In one or more embodiments of the present invention a preferred non limiting example of the chelating agent is EDTA. Typically, the chelating and sequestering agent is present in the composition at a level of up to about 5.0%, preferably 1.0 percent, by weight, of the composition.

Combinations of Modulating Agents may be a useful aspect of the present invention. For example, as will be appreciated by a man of the art combinations of a strong acid and a weak base; a weak acid and a strong base; a weak acid and a strong acid; a weak base and a strong base; a weak base and a second weak base; and a weak acid and a second weak acid; may prove more effective in protecting or stabilizing an active agent in the waterless solvents of the present invention than a base or acid on its own. It will be understood that each of the active agents may have an artificial pH at which it can be more stable in a waterless composition. For example, ascorbic acid in aqueous solution is known to be more stable at an acidic pH of about 5.4. It is therefore desirable to add a combination of modulating agents in a waterless composition that will generate an artificial pH approximately of the order of or equivalent to that at which ascorbic acid is more stable in a waterless medium. In order to do so it will be appreciated a man of the art that that some adjustment will have to be made as ascorbic acid is itself a strong acid and displays the characteristics of a modulating agent. Similarly chelating agents may be usefully

used in combination with another modulating agent such as an acid, a base or a buffer system or with various combinations of modulating agents.

The modulating agent to the foamable composition of the present invention is further useful for adjusting the pH of the target area of application. Skin is the first line of defense against all elements, such as microorganisms, wind, and pollutants, and it's the acid mantle, a fine film with a slightly acidic pH on the surface of the skin that provides protection for the skin. It plays a very important role as an integral part of the barrier function of the stratum corneum. Recent studies have demonstrated that increased enzyme activity of phospholipase A2 is related to the formation of the acid mantle in the stratum corneum. This combination makes the skin less permeable to water and other polar compounds. Normal skin surface pH is between 4 and 6.5 in healthy people, though it varies among the different areas of the skin. Newborn infants do have a higher skin surface pH compared to adults, but this normalizes within three days. Therefore, it is important to maintain skin surface pH in order to prevent susceptibility to bacterial skin infections or skin damage and disease. Thus, adding a modulating agent, which contributes to the stabilization of skin pH at the desirable level, is advantageous.

In the same fashion, adding an acidic modulating agent to a foamable composition, which is intended for vaginal application is advantageous, since the best protection against vaginal infection is attained in pH lower than 4.

While the organic modulating agent can serve to stabilize an active agent in the foam composition, it often provides additional therapeutic properties to the composition. The following table exemplifies, in a non-limiting fashion, the therapeutic benefits expected from an organic modulating agent. It is to be understood that this table provides a non-exhaustive list of modulating agents that possess therapeutic effects, however, many other compounds listed in the present specification also possess therapeutic benefits.

Class	Examples	Exemplary therapeutic properties
Alpha hydroxy acids	Lactic acid Glycolic acid	Humectant Keratocyte growth modifier Anti-psoriasis Anti acne
Beta hydroxyl acid	Salicylic acid	Keratolytic Antiinflammatory Antiinfective
Short chain carboxylic acid	Propionic acid Butyric acid	
Fatty acids	Nonanoic acid Behenic acid	Hair growth stimulant Antiinflammatory Antiinfective Humectant Skin protection
Unsaturated fatty acids	Omega-3 fatty acids Omega-6 fatty acids	Radical scavenger Anti-oxidant
Aromatic acids	Benzoic acid Phthalic acid Nicotinic acid	Antiinflammatory Anti-acne Anti-pigmentation Antiinfective Insect repellent
Dicarboxylic acids	Malonic acid, succinic acid, glutaric acid, adipic acid, pimelic acid, suberic acid, azelaic acid, sebacic acid	Antiinflammatory Keratolytic Anti-acne Anti-rosacea Anti-pigmentation
Amino acids		Keratocyte growth modifier Hair growth stimulant Sebum control

-continued

Class	Examples	Exemplary therapeutic properties
Retinoids	Retinoic acid Isotretinoin	Antiinflammatory Keratolytic Anti-acne Anti-rosacea Anti-pigmentation
Nitrogen containing	Urea	Humectant Keratolytic Anti-psoriasis

In one or more embodiments, the modulating agent may also be a preservative or an antioxidant or an ionization agent. Any preservative, antioxidant or ionization agents suitable for pharmaceutical or cosmetic application may be used. Non limiting examples of antioxidants are tocopherol succinate, propyl galate, butylated hydroxy toluene and butyl hydroxy anisol. Ionization agents may be positive or may be negative depending on the environment and the active agent or composition that is to be protected. Ionization agents may for example act to protect or reduce sensitivity of active agents. Non limiting examples of positive ionization agents are benzyl conium chloride, and cetyl pyridium chloride. Non limiting examples of negative ionization agents are sodium lauryl sulphate, sodium lauryl lactylate and phospholipids.

In one or more embodiments the modulating agent is a flavonoid.

Flavonoids (or bioflavonoids) are a large group of polyphenolic antioxidant compounds, which often occur as glycosides and are ubiquitously present in foods of plant origin. Some flavonoids (e.g. quercetin, rutin) are available as dietary supplements. Flavonoids can be further subdivided into:

- flavonols (e.g. kaempferol, quercetin and myricetin)
- flavones (e.g. apigenin and luteolin)
- flavonones (e.g. hesperetin, naringenin, eriodictyol)
- flavan-3-ols (e.g. (+)-catechin, (+)-gallo catechin, (-)-epicatechin, (-)-epigallocatechin)
- anthocyanins (e.g. cyanidin, delphinidin, malvidin, pelargonidin, peonidin, petunidin)
- proanthocyanidins.

More than 4000 flavonoids have been identified, and many have been studied. Most are colorless but some are responsible for the bright colors of many fruit and vegetables. Flavonoids are distinguished from the carotenoids.

Flavonoids appear to

- act as scavengers of free radicals, including superoxide anions, singlet oxygen, and lipid peroxy radicals (they have antioxidant properties);

- sequester metal ions;

- inhibit in vitro oxidation of LDL cholesterol;

- inhibit cyclo-oxygenase, leading to lower platelet aggregation, decreased thrombotic tendency and reduced anti-inflammatory activity;

- inhibit histamine release;

- improve capillary function by reducing fragility of capillary walls and thus preventing abnormal leakage; and
- inhibit various stages of tumor development (animal studies only).

The activities of flavonoids are dependent on their chemical structure. Estimates of dietary flavonoid intake vary from 10 to 100 mg daily, but may be several hundreds of milligrams a day. Dietary supplements of quercetin and rutin provide around 500 mg in a single dose.

Flavonoids may have a potential role in the prevention of CVD, cancer and cataracts and possibly other diseases, for

anti-viral activity, and they may be useful in treating ulcers. include hemorrhoids, allergy, asthma, menopausal symptoms and the prevention of habitual abortion.

Quercetin

As a dietary supplement, quercetin is promoted for prevention and treatment of atherosclerosis and hyperlipidaemia, diabetes, cataracts, hay fever, peptic ulcer, inflammation, prevention of cancer and for treating prostatitis. A preliminary, double-blind, placebo-controlled trial in chronic non-bacterial prostatitis showed that quercetin reduced pain and improved quality of life, but had no effect on voiding dysfunction.

Rutin

As a dietary supplement, rutin is used to reduce capillary permeability and treat symptoms of varicose veins. In combination with bromelain and trypsin, rutin is used to treat osteoarthritis.

A non limiting list of flavonoid compounds is: benzquericin, diosmin, ethoxazurutoside, flavodate, sodium hesperidin, leucocianido, monoxerutin, oxerutin, quercetin, rutoside, rosmarinic acid. The above information was noted from Dietary Supplements, Electronic Version, Pharmaceutical Press 2007.

In an embodiment a single flavonoid is provided and in a further embodiment a combination of two or more flavonoid are provided. In certain embodiments the flavonoids act synergistically. In an embodiment water soluble flavonoids are combined with water insoluble flavonoids. It is known for example that whole polyphenolic extracts have greater antioxidant effect than their known individual components. In an embodiment flavonoids are used in combination with other phenolics. In an embodiment one or more flavonoids are provided in combination with one or more vitamins. In an embodiment flavonoids are provided that are more reactive than the vitamins. In an embodiment the flavonoids act as a conservational agent.

Microsponges

The Microsponges are rigid, porous and spongelike round microscopic particles of cross-linked polymer beads (e.g., polystyrene or copolymers thereof), each defining a substantially noncollapsible pore network. The Microsponges can be loaded with an active ingredient and can provide a controlled time release of the active ingredient to skin or to a mucosal membrane upon application of the formulation. The slow release is intended to reduce irritation by the active. Microsponge® delivery technology was developed by Advanced Polymer Systems. In one or more embodiments the composition comprises one or more active agents loaded into Microsponges with a waterless carrier comprising a modulating agent.

Polymeric Agent

The composition of the present invention contains a polymeric agent. It has been documented that the presence of a polymeric agent is necessary for the creation of foam, having fine bubble structure, which does not readily collapse upon release from the pressurized aerosol can. The polymeric agent serves to stabilize the foam composition and to control drug residence in the target organ. Preferably, the polymeric agent is soluble or readily dispersible in the polyol; or in the mixture of a polyol and an additional polar solvent.

Non-limiting examples of polymeric agents that are soluble or readily dispersible in propylene glycol are Hydroxypropylcellulose and carbomer (homopolymer of acrylic acid is crosslinked with an allyl ether pentaerythritol, an allyl ether of sucrose, or an allyl ether of propylene, such as Carbopol® 934, Carbopol® 940, Carbopol® 941, Carbopol® 980 and Carbopol® 981.

Other polymeric agents are suitable for use according to the present invention provided that they are soluble or readily dispersible in the polyol; or in the mixture of a polyol and an additional polar solvent, on a case by case basis.

Exemplary polymeric agents include, in a non-limiting manner, naturally-occurring polymeric materials, such as locust bean gum, sodium alginate, sodium caseinate, egg albumin, gelatin agar, carrageenin gum, sodium alginate, xanthan gum, quince seed extract, tragacanth gum, guar gum, cationic guar, hydroxypropyl guar gum, starch, amine-bearing polymers such as chitosan; acidic polymers obtainable from natural sources, such as alginic acid and hyaluronic acid; chemically modified starches and the like, carboxyvinyl polymers, polyvinylpyrrolidone, polyvinyl alcohol, polyacrylic acid polymers, polymethacrylic acid polymers, polyvinyl acetate polymers, polyvinyl chloride polymers, polyvinylidene chloride polymers and the like.

Additional exemplary polymeric agents include semi-synthetic polymeric materials such as cellulose ethers, such as, hydroxypropyl cellulose, Polyethylene glycol, having molecular weight of 1000 or more (e.g., PEG 1,000, PEG 4,000, PEG 6,000 and PEG 10,000) also have gelling capacity and while they are considered herein as "secondary polar solvents", as detailed herein, they are also considered polymeric agents.

Mixtures of the above polymeric agents are contemplated.

The concentration of the polymeric agent should be selected so that the composition, after filling into aerosol canisters, is flowable, and can be shaken in the canister. In one or more embodiments, the concentration of the polymeric agent is selected such that the viscosity of the composition, prior to filling of the composition into aerosol canisters, is less than 12,000 CPs, and more preferably, less than 10,000 CPs.

Surface-Active Agent

The composition further contains a surface-active agent. Surface-active agents (also termed "surfactants") include any agent linking oil and water in the composition, in the form of emulsion. A surfactant's hydrophilic/lipophilic balance (HLB) describes the emulsifier's affinity toward water or oil. HLB is defined for non-ionic surfactants. The HLB scale ranges from 1 (totally lipophilic) to 20 (totally hydrophilic), with 10 representing an equal balance of both characteristics. Lipophilic emulsifiers form water-in-oil (w/o) emulsions; hydrophilic surfactants form oil-in-water (o/w) emulsions. The HLB of a blend of two emulsifiers equals the weight fraction of emulsifier A times its HLB value plus the weight fraction of emulsifier B times its HLB value (weighted average). In many cases a single surfactant may suffice. In other cases a combination of two or more surfactants is desired. Reference to a surfactant in the specification can also apply to a combination of surfactants or a surfactant system. As will be appreciated by a person skilled in the art which surfactant or surfactant system is more appropriate is related to the vehicle and intended purpose. In general terms a combination of surfactants can be significant in producing breakable forms of good quality. It has been further discovered that the generally thought considerations for HLB values for selecting a surfactant or surfactant combination are not always binding for emulsions and moreover for waterless and substantially non aqueous carriers the usual guidelines are less applicable. Surfactants also play a significant role in foam formation where the foamable formulation is a single phase composition.

According to one or more embodiments the composition contains a single surface active agent having an HLB value between about 2 and 9, or more than one surface active agent and the weighted average of their HLB values is between about 2 and about 9.

According to one or more embodiments the composition contains a single surface active agent having an HLB value between about 7 and 14, or more than one surface active agent and the weighted average of their HLB values is between about 7 and about 14.

According to one or more other embodiments the composition contains a single surface active agent having an HLB value between about 9 and about 19, or more than one surface active agent and the weighted average of their HLB values is between about 9 and about 19.

In a waterless or substantially waterless environment a wide range of HLB values may be suitable.

Preferably, the composition contains a non-ionic surfactant. Nonlimiting examples of possible non-ionic surfactants include a polysorbate, polyoxyethylene (20) sorbitan monostearate, polyoxyethylene (20) sorbitan monooleate, a polyoxyethylene fatty acid ester, Myrj 45, Myrj 49, Myrj 52 and Myrj 59; a polyoxyethylene alkyl ether, polyoxyethylene cetyl ether, polyoxyethylene palmityl ether, polyethylene oxide hexadecyl ether, polyethylene glycol cetyl ether, steareths such as steareth 2, brij 21, brij 721, brij 38, brij 52, brij 56 and brij W1, a sucrose ester, a partial ester of sorbitol and its anhydrides, sorbitan monolaurate, sorbitan monolaurate, a monoglyceride, a diglyceride, isoceteth-20 and mono-, di- and tri-esters of sucrose with fatty acids. In certain embodiments, suitable sucrose esters include those having high monoester content, which have higher HLB values.

In an embodiment the surfactant is an ether for example polyoxyethylene (26) glycerol ether.

In certain embodiments, surfactants are selected which can provide a close packed surfactant layer. To achieve such objectives combinations of at least two surfactants are selected. Preferably, they should be complex emulgators and more preferably they should both be of a similar molecular type; for example, a pair of ethers, like steareth 2 and steareth 21, or a pair of esters, for example, PEG-40 stearate and polysorbate 80. Ideally, the surfactants can be ethers. In certain circumstances POE esters cannot be used and a combination of sorbitan laurate and sorbitan stearate or a combination of sucrose stearic acid ester mixtures and sodium laurate may be used. All these combinations due to their versatility and strength may also be used satisfactorily and effectively with ether formulations, although the amounts and proportion may be varied according to the formulation and its objectives as will be appreciated by a man of the art.

It has been discovered also that by using a derivatized hydrophilic polymer with hydrophobic alkyl moieties as a polymeric emulsifier such as pemulen it is possible to stabilize the emulsion better about or at the region of phase reversal tension. Other types of derivatized polymers like silicone copolymers, derivatized starch [Aluminum Starch Octenylsuccinate (ASOS)]/[DRY-FLO AF Starch], and derivatized dextrin may also a similar stabilizing effect.

A series of dextrin derivative surfactants prepared by the reaction of the propylene glycol polyglucosides with a hydrophobic oxirane-containing material of the glycidyl ether are highly biodegradable. [Hong-Rong Wang and Keng-Ming Chen, Colloids and Surfaces A: Physicochemical and Engineering Aspects Volume 281, Issues 1-3, 15 Jun. 2006, Pages 190-193].

Non-limiting examples of non-ionic surfactants that have HLB of about 7 to about 12 include steareth 2 (HLB~4.9); glyceryl monostearate/PEG 100 stearate (Av HLB~11.2); steareth Laureth 4 (HLB~9.7) and cetomacrogol ether (e.g., polyethylene glycol 1000 monocetyl ether).

Non-limiting examples of preferred surfactants, which have a HLB of 4-19 are set out in the Table below:

Surfactant	HLB
steareth 2	~4.9
glyceryl monostearate/PEG 100 stearate	Av ~11.2
Glyceryl Stearate	~4
Steareth-21	~15.5
peg 40 stearate	~16.9
polysorbate 80	~15
sorbitan stearate	~4.7
laureth 4	~9.7
Sorbitan monooleate (span 80)	~4.3
ceteareth 20	~15.7
steareth 20	~15.3
ceteth 20	~15.7
Macrogol Cetostearyl Ether	~15.7
ceteth 2 (Lipocol C-2)	~5.3
PEG-30 Dipolyhydroxystearate	~5.5
sucrose distearate (Sisterna SP30)	~6
polyoxyethylene (100) stearate	~18.8

More exemplary stabilizing surfactants which may be suitable for use in the present invention are found below.

PEG-Fatty Acid Monoester Surfactants		
Chemical name	Product example name	HLB
PEG-30 stearate	Myrj 51	>10
PEG-40 laurate	Crodet L40 (Croda)	17.9
PEG-40 oleate	Crodet O40 (Croda)	17.4
PEG-45 stearate	Nikkol MYS-45 (Nikko)	18
PEG-50 stearate	Myrj 53	>10
PEG-100 stearate	Myrj 59, Arlcel 165 (ICI)	19

PEG-Fatty Acid Diester Surfactants:		
Chemical name	Product example name	HLB
PEG-4 dilaurate	Mapeg .RTM. 200 DL (PPG), Kessco .RTM.PEG 200 DL (Stepan), LIPOPEG 2-DL (Lipo Chem.)	7
PEG-4	distearate Kessco .RTM. 200 DS (Stepan.sub)	5
PEG-32 dioleate	Kessco .RTM. PEG 1540 DO (Stepan)	15
PEG-400 dioleate	Cithrol 4DO series (Croda)	>10
PEG-400 disterate	Cithrol 4DS series (Croda)	>10
PEG-20 glyceryl oleate	Tagat .RTM. O (Goldschmidt)	>10

Transesterification Products of Oils and Alcohols		
Chemical name	Product example name	HLB
PEG-30 castor oil	Emalex C-30 (Nihon Emulsion)	11
PEG-40 hydrogenated castor oil	Cremophor RH 40 (BASF), Croduret (Croda), Emulgin HRE 40 (Henkel)	13

Polyglycerized Fatty Acids, such as:		
Chemical name	Product example name	LB
Polyglyceryl-6 dioleate	Caprol .RTM. 6G20 (ABITEC); PGO-62 (Calgene), PLUROL OLEIQUE CC 497 (Gattefosse)Hodag	8.5

PEG-Sorbitan Fatty Acid Esters		
Chemical name	Product example name	HLB
5 PEG-20 sorbitan monolaurate	Tween-20 (Atlas/ICI), Crillet 1 (Croda), DACOL MLS 20 (Condea)	17
PEG-20 sorbitan Monopalmitate	Tween 40 (Atlas/ICI), Crillet 2 (Croda)	16
10 PEG-20 sorbitan monostearate	Tween-60 (Atlas/ICI), Crillet 3 (Croda)	15
PEG-20 sorbitan monooleate	Tween-80 (Atlas/ICI), Crillet 4 (Croda)	15

Polyethylene Glycol Alkyl Ethers		
Chemical name	Product example name	HLB
PEG-2 oleyl ether	oleth-2 Brij 92/93 (Atlas/ICI)	4.9
PEG-3 oleyl ether	oleth-3 Volpo 3 (Croda)	<10
PEG-5 oleyl ether	oleth-5 Volpo 5 (Croda)	<10
PEG-10 oleyl ether	oleth-10 Volpo 10 (Croda), Brij 96/97 (Atlas/ICI)	12
PEG-20 oleyl ether	oleth-20 Volpo 20 (Croda), Brij 98/99 (Atlas/ICI)	15
25 PEG-4 lauryl ether	laureth-4Brij 30 (Atlas/ICI)	9.7
PEG-23 lauryl ether	laureth-23Brij 35 (Atlas/ICI)	17
PEG-10 stearyl ether	Brij 76 (ICI)	12
PEG-2 cetyl ether	Brij 52 (ICI)	5.3

Sugar Ester Surfactants		
Chemical name	Product example name	HLB
35 Sucrose distearate	Sisterna SP50, Surfope 1811	11

Sorbitan Fatty Acid Ester Surfactants		
Chemical name	Product example name	HLB
40 Sorbitan monolaurate	Span-20 (Atlas/ICI), Crill 1 (Croda), Arlcel 20 (ICI)	8.6
Sorbitan monopalmitate	Span-40 (Atlas/ICI), Crill 2 (Croda), Nikkol SP-10 (Nikko)	6.7
45 Sorbitan monooleate	Span-80 (Atlas/ICI), Crill 4 (Croda), Crill 50 (Croda)	4.3
Sorbitan monostearate	Span-60 (Atlas/ICI), Crill 3 (Croda), Nikkol SS-10 (Nikko)	4.7

50 In one or more embodiments the surface active agent is a complex emulgator in which the combination of two or more surface active agents can be more effective than a single surfactant and provides a more stable formulation or improved foam quality than a single surfactant. For example and by way of non-limiting explanation it has been found that 55 by choosing say two surfactants, one hydrophobic and the other hydrophilic the combination can produce a more stable emulsion than a single surfactant. Preferably, the complex emulgator comprises a combination of surfactants wherein there is a difference of about 4 or more units between the HLB 60 values of the two surfactants or there is a significant difference in the chemical nature or structure of the two or more surfactants.

Specific non limiting examples of surfactant systems are, 65 combinations of polyoxyethylene alkyl ethers, such as Brij 59/Brij 10; Brij 52/Brij 10; Steareth 2/Steareth 20; Steareth 2/Steareth 21 (Brij 72/Brij 721); combinations of polyoxy-

ethylene stearates such as Myrj 52/Myrj 59; combinations of sucrose esters, such as Surphope 1816/Surphope 1807; combinations of sorbitan esters, such as Span 20/Span 80; Span 20/Span 60; combinations of sucrose esters and sorbitan esters, such as Surphope 1811 and Span 60; combinations of liquid polysorbate detergents and PEG compounds, such as Tween 80/PEG-40 stearate; methyl glucosyl sequestearate; polymeric emulsifiers, such as Permulen (TRI or TR2); liquid crystal systems, such as Arlatone (2121), Stepan (Mild RM1), Nikomulse (41) and Montanov (68) and the like.

In certain embodiments the surfactant is preferably one or more of the following: a combination of steareth-2 and steareth-21 on their own or in combination with glyceryl monostearate (GMS); in certain other embodiments the surfactant is a combination of polysorbate 80 and PEG-40 stearate. In certain other embodiments the surfactant is a combination of glyceryl monostearate/PEG 100 stearate. In certain other embodiments the surfactant is a combination of two or more of stearate 21, PEG 40 stearate, and polysorbate 80. In certain other embodiments the surfactant is a combination of two or more of laureth 4, span80, and polysorbate 80. In certain other embodiments the surfactant is a combination of two or more of GMS and cetareth. In certain other embodiments the surfactant is a combination of two or more of steareth 21, cetareth 20, ceteth 2 and laureth 4. In certain other embodiments the surfactant is a combination of cetareth 20 and polysorbate 40 stearate. In certain other embodiments the surfactant is a combination of span 60 and GMS. In certain other embodiments the surfactant is a combination of two or all of PEG 40 stearate, sorbitan stearate and polysorbate 60.

In certain other embodiments the surfactant is one or more of sucrose stearic acid esters, sorbitan laureth, and sorbitan stearate.

Without being bound by any particular theory or mode of operation, it is believed that the use of non-ionic surfactants with significant hydrophobic and hydrophilic components, increase the emulsifier or foam stabilization characteristics of the composition. Similarly, without being bound by any particular theory or mode of operation, using combinations of surfactants with high and low HLB's to provide a relatively close packed surfactant layer may strengthen the formulation.

In one or more embodiments the stability of the composition can be improved when a combination of at least one non-ionic surfactant having HLB of less than 9 and at least one non-ionic surfactant having HLB of equal or more than 9 is employed. The ratio between the at least one non-ionic surfactant having HLB of less than 9 and the at least one non-ionic surfactant having HLB of equal or more than 9, is between 1:8 and 8:1, or at a ratio of 4:1 to 1:4. The resultant HLB of such a blend of at least two emulsifiers is preferably between about 9 and about 14.

Thus, in an exemplary embodiment, a combination of at least one non-ionic surfactant having HLB of less than 9 and at least one non-ionic surfactant having HLB of equal or more than 9 is employed, at a ratio of between 1:8 and 8:1, or at a ratio of 4:1 to 1:4, wherein the HLB of the combination of emulsifiers is preferably between about 5 and about 18.

In certain cases, the surface active agent is selected from the group of cationic, zwitterionic, amphoteric and ampholytic surfactants, such as sodium methyl cocoyl taurate, sodium methyl oleoyl taurate, sodium lauryl sulfate, triethanolamine lauryl sulfate and betaines.

Many amphiphilic molecules can show lyotropic liquid-crystalline phase sequences depending on the volume balances between the hydrophilic part and hydrophobic part. These structures are formed through the micro-phase segre-

gation of two. Many amphiphilic molecules can show lyotropic liquid-crystalline phase sequences depending on the volume balances between the hydrophilic part and hydrophobic part. These structures are formed through the micro-phase segregation of two incompatible components on a nanometer scale. Soap is an everyday example of a lyotropic liquid crystal. Certain types of surfactants tend to form lyotropic liquid crystals in emulsions interface (oil-in-water) and exert a stabilizing effect.

In one or more embodiments the surfactant is a surfactant or surfactant combination is capable of or which tends to form liquid crystals. Surfactants which tend to form liquid crystals may improve the quality of foams. Non limiting examples of surfactants with postulated tendency to form interfacial liquid crystals are: phospholipids, alkyl glucosides, sucrose esters, sorbitan esters.

In one or more embodiments the at least one surface active agent is liquid. Moreover for the purposes of formulating with liquid ethers a liquid surfactant is preferred.

In one or more embodiments the liquid surfactant is a polysorbate, preferably polysorbate 80 or 60.

In one or more embodiments the at least one surface active agent is solid, semi solid or waxy. In a further embodiment they are soluble in oil and in another embodiment have a HLB of less than about 12.

It should be noted that HLB values may not be so applicable to non ionic surfactants, for example, with liquid crystals or with silicones. Also HLB values may be of lesser significance in a waterless or substantially non-aqueous environment.

In one or more embodiments the surfactant can be, a surfactant system comprising of a surfactant and a co surfactant, a waxy emulsifier, a liquid crystal emulsifier, an emulsifier which is solid or semi solid at room temperature and pressure, or combinations of two or more agents in an appropriate proportion as will be appreciated a person skilled in the art. Where a solid or semi solid emulsifier combination is used it can also comprise a solid or semi solid emulsifier and a liquid emulsifier. In a preferred embodiment at least one surfactant is a liquid.

In one or more embodiments, the surface-active agent includes at least one non-ionic surfactant. Ionic surfactants are known to be irritants. Therefore, non-ionic surfactants are preferred in applications including sensitive tissue such as found in most mucosal tissues, especially when they are infected or inflamed. Non-ionic surfactants alone can provide formulations and foams of good or excellent quality in the carriers and compositions of the present invention.

Thus, in a preferred embodiment, the surface active agent, the composition contains a non-ionic surfactant. In another preferred embodiment the composition includes a mixture of non-ionic surfactants as the sole surface active agent. Yet, in additional embodiments, the foamable composition includes a mixture of at least one non-ionic surfactant and at least one ionic surfactant in a ratio in the range of about 100:1 to 6:1. In one or more embodiments, the non-ionic to ionic surfactant ratio is greater than about 6:1, or greater than about 8:1; or greater than about 14:1, or greater than about 16:1, or greater than about 20:1. In further embodiments, surface active agent comprises a combination of a non-ionic surfactant and an ionic surfactant, at a ratio of between 1:1 and 20:1.

In one or more embodiments, a combination of a non-ionic surfactant and an ionic surfactant (such as sodium lauryl sulphate and cocamidopropylbetaine) is employed, at a ratio of between 1:1 and 20:1, or at a ratio of 4:1 to 10:1; for example, about 1:1, about 4:1, about 8:1, about 12:1, about

16:1 and about 20:1 or at a ratio of 4:1 to 10:1, for example, about 4:1, about 6:1, about 8:1 and about 10:1.

For foams in selecting a suitable surfactant or combination thereof it should be borne in mind that the upper amount of surfactant that may be used may be limited by the shakability of the composition. If the surfactant is non liquid, it can make the formulation to viscous or solid. Subject to its miscibility solid surfactants may be added first, and may require gentle warming and then cooling before being combined with the other ingredients. In general terms, as the amount of non-liquid surfactant is increased the shakability of the formulation reduces until a limitation point is reached where the formulation can become non shakable and unsuitable. Thus in one embodiment, any effective amount of surfactant may be used provided the formulation remains shakable. In other certain limited embodiments the upper limit for foamable formulations may be determined by flowability such that any effective amount can be used provided the formulation is sufficiently flowable to be able to flow through an actuator valve and be released and still expand to form a good quality foam. This may be due without being bound by any theory to one or more of a number of factors such as the viscosity, the softness, the lack of crystals, the pseudoplastic or semi pseudo plastic nature of the composition and the dissolution of the propellant into the composition.

In certain embodiments the amount of surfactant or combination of surfactants is between about 0.05% to about 20%; between about 0.05% to about 15%, or between about 0.05% to about 10%. In a preferred embodiment the concentration of surface active agent is between about 0.2% and about 8%. In a more preferred embodiments the concentration of surface active agent is between about 1% and about 6% or between about 1% and about 4%.

In some embodiments, it is desirable that the surface active agent does not contain a polyoxyethylene (POE) moiety, such as polysorbate surfactants, POE fatty acid esters, and POE alkyl ethers, because the active agent is incompatible with such surface active agents. For example, the active agent pimecrolimus is not stable the presence of POE moieties, yet benefits greatly from the use of dicarboxylic esters as penetration enhancers. In such cases, alternative surface active agents are employed. In an exemplary manner, POE-free surfactants include non-ethoxylated sorbitan esters, such as sorbitan monopalmitate, sorbitan monostearate, sorbitan tristearate, sorbitan monooleate, sorbitan trioleate, sorbitan monolaurate and sorbitan sesquioleate; glycerol fatty acid esters, such as glycerol monostearate and glycerol monooleate; mono-, di- and tri-esters of sucrose with fatty acids (sucrose esters), sucrose stearate, sucrose distearate sucrose palmitate and sucrose laurate; and alkyl polyglycosides, such as lauryl diglucoside.

In one or more embodiments, the surface-active agent includes mono-, di- and tri-esters of sucrose with fatty acids (sucrose esters), prepared from sucrose and esters of fatty acids or by extraction from sucro-glycerides. Suitable sucrose esters include those having high monoester content, which have higher HLB values.

In one or more preferred embodiments of the present invention the surfactant includes at least one surfactant selected from a polyoxyethylene fatty ether, a polyoxyethylene fatty ester, a carbohydrate ester and a sucrose ester.

In one or more embodiments non limiting examples of non-ionic surfactants include steareth-2, steareth-20, steareth-21, cetareth 2, PEG-100 stearyl ether, cetearyl glucoside, methyl glucose sesquisteate, sorbitan monostearate, GMS NE and span 20.

In one or more embodiments non limiting other examples of surfactant combinations are glyceryl stearate and PEG 100 stearate and laureth 4; steareth 2, PEG 100 searate and laureth 4; and cetearyl glucoside and cetearyl alcohol.

In an embodiment the surfactant containing formulations are further boosted by a foam adjuvant for example stearyl alcohol.

A non limiting example of a combination of surfactants having a weighted average of their HLB values of 11 is Glyceryl Stearate and PEG-100 Stearate (for example trade name "simulsol 165" from Sepic).

Hydrophobic Solvent

Optionally, the foamable carrier further contains at least one hydrophobic solvent. The identification of a "hydrophobic solvent", as used herein, is not intended to characterize the solubilization capabilities of the solvent for any specific active agent or any other component of the foamable composition. Rather, such information is provided to aid in the identification of materials suitable for use as a part in the foamable compositions described herein.

A "hydrophobic solvent" as used herein refers to a material having solubility in distilled water at ambient temperature of less than about 1 gm per 100 mL, more preferable less than about 0.5 gm per 100 mL, and most preferably less than about 0.1 gm per 100 mL.

In one or more embodiments, the hydrophobic organic carrier is an oil, such as mineral oil, isopropyl palmitate, isopropyl isostearate, diisopropyl adipate, diisopropyl dimerate, maleated soybean oil, octyl palmitate, cetyl lactate, cetyl ricinoleate, tocopheryl acetate, acetylated lanolin alcohol, cetyl acetate, phenyl trimethicone, glyceryl oleate, tocopheryl linoleate, wheat germ glycerides, arachidyl propionate, myristyl lactate, decyl oleate, propylene glycol ricinoleate, isopropyl lanolate, pentaerythrityl tetraestearate, neopentylglycol dicaprylate/dicaprate, isononyl isononanoate, isotridecyl isononanoate, myristyl myristate, triisocetyl citrate, octyl dodecanol, unsaturated or polyunsaturated oils, such as olive oil, corn oil, soybean oil, canola oil, cottonseed oil, coconut oil, sesame oil, sunflower oil, borage seed oil, syzigium aromaticum oil, hempseed oil, herring oil, cod-liver oil, salmon oil, flaxseed oil, wheat germ oil, evening primrose oils; essential oils; and silicone oils, such as dimethicone, cyclomethicone, polyalkyl siloxanes, polyaryl siloxanes, polyalkylaryl siloxanes and polyether siloxane copolymers, polydimethylsiloxanes (dimethicones) and poly(dimethylsiloxane)-(diphenyl-siloxane) copolymers. In one or more further embodiments the hydrophobic organic carrier is petrolatum.

Humectant

A humectant, is a substance that helps retain moisture and also prevents rapid evaporation. Non limiting examples of suitable humectants are propylene glycol, propylene glycol derivatives, and glycerin. Other examples of humectants and moisturizers may be found in the Handbook of Pharmaceutical Additives published by Gower. Suitable ones for use with and soluble in the waterless compositions of the present invention may be selected as will be appreciated by a person skilled in the art.

Moisturizers

A moisturizer, is a substance that helps retain moisture or add back moisture to the skin. Examples are allantoin, petrolatum, urea, lactic acid, sodium PCV, glycerin, shea butter, caprylic/capric/stearic triglyceride, candelilla wax, propylene glycol, lanolin, hydrogenated oils, squalene, sodium hyaluronate and lysine PCA. Glycerine and sodium pCA work in combination. Other examples may be found in the Handbook of Pharmaceutical Additives published by Gower.

Pharmaceutical compositions of the present invention may in one or more embodiments usefully comprise in addition a humectant or a moisturizer or combinations thereof.

Foam Adjuvant

Optionally, a foam adjuvant is included in the foamable carriers of the present invention to increase the foaming capacity of surfactants and/or to stabilize the foam. In one or more embodiments of the present invention, the foam adjuvant agent includes fatty alcohols having 15 or more carbons in their carbon chain, such as cetyl alcohol and stearyl alcohol (or mixtures thereof). Other examples of fatty alcohols are arachidyl alcohol (C20), behenyl alcohol (C22), 1-triacontanol (C30), as well as alcohols with longer carbon chains (up to C50). Fatty alcohols, derived from beeswax and including a mixture of alcohols, a majority of which has at least 20 carbon atoms in their carbon chain, are especially well suited as foam adjuvant agents. The amount of the fatty alcohol required to support the foam system is inversely related to the length of its carbon chains. Foam adjuvants, as defined herein are also useful in facilitating improved spreadability and absorption of the composition.

In one or more embodiments of the present invention, the foam adjuvant agent includes fatty acids having 16 or more carbons in their carbon chain, such as hexadecanoic acid (C16) stearic acid (C18), arachidic acid (C20), behenic acid (C22), octacosanoic acid (C28), as well as fatty acids with longer carbon chains (up to C50), or mixtures thereof. As for fatty alcohols, the amount of fatty acids required to support the foam system is inversely related to the length of its carbon chain.

Optionally, the carbon atom chain of the fatty alcohol or the fatty acid may have at least one double bond. A further class of foam adjuvant agent includes a branched fatty alcohol or fatty acid. The carbon chain of the fatty acid or fatty alcohol also can be substituted with a hydroxyl group, such as 12-hydroxy stearic acid.

Additional Components

In an embodiment of the present invention, a composition of the present invention includes one or more additional components. Such additional components include but are not limited to anti perspirants, anti-static agents, buffering agents, bulking agents, chelating agents, cleansers, colorants, conditioners, deodorants, diluents, dyes, emollients, fragrances, hair conditioners, humectants, pearlescent aids, perfuming agents, permeation enhancers, pH-adjusting agents, preservatives, protectants, skin penetration enhancers, softeners, solubilizers, sunscreens, sun blocking agents, sunless tanning agents, viscosity modifiers and vitamins and flavonoids. As is known to one skilled in the art, in some instances a specific additional component may have more than one activity, function or effect.

In an embodiment of the present invention, the additional component is a pH adjusting agent or a buffering agent. Suitable buffering agents include but are not limited to acetic acid, adipic acid, calcium hydroxide, citric acid, glycine, hydrochloric acid, lactic acid, magnesium aluminometasilicates, phosphoric acid, sodium carbonate, sodium citrate, sodium hydroxide, sorbic acid, succinic acid, tartaric acid, and derivatives, salts and mixtures thereof.

In an embodiment of the present invention, the additional component is an emollient. Suitable emollients include but are not limited to mineral oil, lanolin oil, coconut oil, cocoa butter, olive oil, aloe vera extract, jojoba oil, castor oil, fatty acids, fatty alcohols, diisopropyl adipate, hydroxybenzoate esters, benzoic acid esters of C9 to C15 alcohols, isononyl iso-nonanoate, silicone oils, polyethers, C12 to C15 alkyl benzoates, oleic acid, stearic fatty acid, cetyl alcohols, hexa-

decyl alcohol, dimethyl polysiloxane, polyoxypropylene cetyl ether, polyoxypropylene butyl ether, and derivatives, esters, salts and mixtures thereof.

In an embodiment of the present invention, the additional component is a humectant. Suitable humectants include but are not limited to guanidine, urea, glycolic acid, glycolate salts, ammonium glycolate, quaternary alkyl ammonium glycolate, lactic acid, lactate salts, ammonium lactate, quaternary alkyl ammonium lactate, aloe vera, aloe vera gel, allantoin, urazole, alkoxylated glucose, hyaluronic acid, lactamide monoethanolamine, acetamide monoethanolamine and derivatives, esters, salts and mixtures thereof.

In an embodiment of the present invention, the additional component is a preservative. Suitable preservatives include but are not limited to C12 to C15 alkyl benzoates, alkyl p-hydroxybenzoates, aloe vera extract, ascorbic acid, benzalkonium chloride, benzoic acid, benzoic acid esters of C9 to C15 alcohols, butylated hydroxytoluene, castor oil, cetyl alcohols, chlorocresol, citric acid, cocoa butter, coconut oil, diazolidinyl urea, diisopropyl adipate, dimethyl polysiloxane, DMDM hydantoin, ethanol, fatty acids, fatty alcohols, hexadecyl alcohol, hydroxybenzoate esters, iodopropenyl butylcarbamate, isononyl iso-nonanoate, jojoba oil, lanolin oil, methylparaben, mineral oil, oleic acid, olive oil, polyethers, polyoxypropylene butyl ether, polyoxypropylene cetyl ether, potassium sorbate, silicone oils, sodium propionate, sodium benzoate, sodium bisulfite, sorbic acid, stearic fatty acid, vitamin E, vitamin E acetate and derivatives, esters, salts and mixtures thereof.

In an embodiment of the present invention, the additional component is a skin penetration enhancer. Suitable skin penetration enhancers include but are not limited to acetone, acyl lactylates, acyl peptides, acylsarcosinates, alkanolamine salts of fatty acids, alkyl benzene sulphonates, alkyl ether sulphates, alkyl sulphates, anionic surface-active agents, benzyl benzoate, benzyl salicylate, butan-1,4-diol, butyl benzoate, butyl laurate, butyl myristate, butyl stearate, cationic surface-active agents, citric acid, cocoamidopropylbetaine, decyl methyl sulfoxide, decyl oleate, dibutyl azelate, dibutyl phthalate, dibenzyl sebacate, dibutyl sebacate, dibutyl suberate, dibutyl succinate, dicapryl adipate, didecyl phthalate, diethylene glycol, diethyl sebacate, diethyl-m-toluamide, di(2-hydroxypropyl) ether, diisopropyl adipate, diisopropyl sebacate, N,N-dimethyl acetamide, dimethyl azelate, N,N-dimethyl formamide, 1,5-dimethyl-2-pyrrolidone, dimethyl sebacate, dimethyl sulphoxide, dioctyl adipate, dioctyl azelate, dioctyl sebacate, 1,4 dioxane, 1-dodecylazacycloheptan-2-one, dodecyl dimethyl amine oxides, ethyl caprate, ethyl caproate, ethyl caprylate, 2-ethyl-hexyl pelargonate, ethyl-2-hydroxypropanoate, ethyl laurate, ethyl myristate, 1-ethyl-2-pyrrolidone, ethyl salicylate, hexyl laurate, 2-hydroxyoctanoic acid, 2-hydroxypropanoic acid, 2-hydroxypropionic acid, isethionates, isopropyl isostearate, isopropyl palmitate, guar hydroxypropyltrimonium chloride, hexan-2,5-diol, khellin, lamepons, lauryl alcohol, maypons, metal salts of fatty acids, methyl nicotinate, 2-methyl propan-2-ol, 1-methyl-2-pyrrolidone, 5-methyl-2-pyrrolidone, methyl taurides, miranol, nonionic surface-active agents, octyl alcohol, octylphenoxy polyethoxyethanol, oleic ethanolamide, pleyl alcohol, pentan-2,4-diol, phenoxyethanol, phosphatidyl choline, phosphine oxides, polyalkoxylated ether glycolates, poly(diallylpiperidinium chloride), poly(dipropyldiallylammonium chloride), polyglycerol esters, polyoxyethylene lauryl ether, polyoxy-polyoxyethylene stearate, polyoxypropylene 15 stearyl ether, poly(vinyl pyridinium chloride), propan-1-ol, propan-2-ol, propylene glycol dipelargonate, pyroglutamic acids, 2-pyrrolidone, pyruvic acids, Quater-

nium 5, Quaternium 18, Quaternium 19, Quaternium 23, Quaternium 31, Quaternium 40, Quaternium 57, quaternary amine salts, quaternised poly (dimethylaminoethyl-methacryl-ate), quaternised poly (vinyl alcohol), saponin hydrochloride, sodium cocaminopropionate, sodium dioctyl sulphonsuccinate, sodium laurate, sodium lauryl ether sulphate, sodium lauryl sulphate, sugar esters, sulphosuccinate, tetrahydrofuran, tetrahydrofurfural alcohol, transcitol, triethanolamine dodecyl benzene sulphonate, triethanolamine oleate, urea, water and derivatives, esters, salts and mixtures thereof.

In an embodiment the composition with modulating agent may be used as is without addition of a propellant. In other embodiments propellant is added to form a foamable composition that produces a foam when the formulation is expelled from a pressurized canister. The foam may be of various qualities as indicated herein. In a preferred embodiment the foam is of about good quality. In a more preferred embodiment it is of about excellent quality.

Propellants

Examples of suitable propellants include volatile hydrocarbons such as butane, propane, isobutane and fluorocarbon gases, or mixtures thereof.

In an embodiment the propellant is AP 70 which is a mixture of propane, isobutene and butane.

The propellant makes up about 5-25 wt % of the foamable composition. In some circumstances the propellant may be up to 35%. The propellants are used to generate and administer the foamable composition as a foam. The total composition including propellant, foamable compositions and optional ingredients is referred to as the foamable composition.

Alcohol and organic solvents render foams inflammable. It has been surprisingly discovered that fluorohydrocarbon propellants, other than chloro-fluoro carbons (CMCs), which are non-ozone-depleting propellants, are particularly useful in the production of a non-flammable foamable composition. A test according to European Standard prEN 14851, titled "Aerosol containers—Aerosol foam flammability test" revealed that compositions containing an organic carrier that contains a hydrophobic organic carrier and/or a polar solvent, which are detected as inflammable when a hydrocarbon propellant is used, become non-flammable, while the propellant is an HFC propellant.

Such propellants include, but are not limited to, hydrofluorocarbon (HFC) propellants, which contain no chlorine atoms, and as such, fall completely outside concerns about stratospheric ozone destruction by chlorofluorocarbons or other chlorinated hydrocarbons. Exemplary non-flammable propellants according to this aspect of the invention include propellants made by DuPont under the registered trademark Dymel, such as 1,1,1,2 tetrafluoroethane (Dymel 134), and 1,1,1,2,3,3,3 heptafluoropropane (Dymel 227) 1,1, difluoro ethane (Dymel 152) and 1,1,1,3,3,3 hexafluoropropane HFCs possess Ozone Depletion Potential of 0.00 and thus, they are allowed for use as propellant in aerosol products.

Notably, the stability of foamable emulsions including HFC as the propellant can be improved in comparison with the same composition made with a hydrocarbon propellant.

In one or more embodiments foamable compositions comprise a combination of a HFC and a hydrocarbon propellant such as n-butane or mixtures of hydrocarbon propellants such as propane, isobutane and butane.

Composition and Foam Physical Characteristics and Advantages

A pharmaceutical or cosmetic composition manufactured using the foamable carrier of the present invention is very easy to use. When applied onto the afflicted body surface of

mammals, i.e., humans or animals, it is in a foam state, allowing free application without spillage. Upon further application of a mechanical force, e.g., by rubbing the composition onto the body surface, it freely spreads on the surface and is rapidly absorbed.

The foamable composition of the present invention is stable, having an acceptable shelf-life of months or preferably at least one year, or more preferably, at least two years at ambient temperature, as revealed in accelerated stability tests. Organic carriers and propellants tend to impair the stability of emulsions and to interfere with the formation of stable foam upon release from a pressurized container. It has been observed, however, that the foamable compositions according to the present invention are surprisingly stable. Following accelerated stability studies, they demonstrate desirable texture; they form fine bubble structures that do not break immediately upon contact with a surface, spread easily on the treated area and absorb quickly.

The composition should also be free flowing, to allow it to flow through the aperture of the container, e.g., and aerosol container, and create an acceptable foam.

Foam quality can be graded as follows:

Grade E (excellent): very rich and creamy in appearance, does not show any bubble structure or shows a very fine (small) bubble structure; does not rapidly become dull; upon spreading on the skin, the foam retains the creaminess property and does not appear watery.

Grade G (good): rich and creamy in appearance, very small bubble size, "dulls" more rapidly than an excellent foam, retains creaminess upon spreading on the skin, and does not become watery.

Grade FG (fairly good): a moderate amount of creaminess noticeable, bubble structure is noticeable; upon spreading on the skin the product dulls rapidly and becomes somewhat lower in apparent viscosity.

Grade F (fair): very little creaminess noticeable, larger bubble structure than a "fairly good" foam, upon spreading on the skin it becomes thin in appearance and watery.

Grade P (poor): no creaminess noticeable, large bubble structure, and when spread on the skin it becomes very thin and watery in appearance.

Grade VP (very poor): dry foam, large very dull bubbles, difficult to spread on the skin.

Typically administrable foams are typically of quality grade E or G, when released from the aerosol container. Smaller bubbles are indicative of more stable foam, which does not collapse spontaneously immediately upon discharge from the container. The finer foam structure looks and feels smoother, thus increasing its usability and appeal.

A further aspect of the foam is breakability. Thermally sensitive foams immediately collapse upon exposure to skin temperature and, therefore, cannot be applied on the hand and afterwards delivered to the afflicted area.

The foam of the present invention has several advantages, when compared with hydroalcoholic foam compositions, such as

- (1) Breakability. The foam of the present invention is thermally stable and breakable under sheer force but is not "quick breaking which allows comfortable application and well directed administration to the target area;
- (2) Skin drying and skin barrier function. Short chain alcohols are known to dry the skin and impair the integrity of the skin barrier. By contrast, including a film forming agent in the composition of the present invention does not cause unwanted skin barrier damage; and

(3) Irritability. Due to the lack of alcohol and improvement in skin barrier function, skin irritability is eliminated or reduced.

Another property of the foam is specific gravity, as measured upon release from the aerosol can. Typically, foams have specific gravity of less than 0.12 g/mL; or less than 0.10 g/mL; or less than 0.08 g/mL, depending on their composition and on the propellant concentration.

Pharmaceutical Composition

The compositions, the foamable compositions and the foams of the present invention are ideal vehicles for active pharmaceutical ingredients and active cosmetic ingredients. In the context of the present invention, active pharmaceutical ingredients and active cosmetic ingredients are collectively termed "active agent" or "active agents". A foamable composition, comprising an active agent has the following advantages:

1. The foamable composition provides a preferred solvent for active agents, particularly water-insoluble agents.
2. The inclusion of a polyol and/or a PEG and a secondary polar solvent in the foamable composition facilitates a co-solvent effect, resulting increased concentrations of soluble active agent in the dosage form, thus facilitating enhanced skin penetration of the active agent. In many cases, increased penetration is positively correlated with improved clinical outcome. In certain case, attaining an increased drug penetration into the target site of action enables a decrease of treatment frequency, for example, from twice or three times daily to once daily.
3. Polyols and PEGs; and combinations of a polyol and/or PEG with a secondary polar solvent are known as skin penetration enhancers, thus, increasing drug residence in the target area and increasing clinical efficacy, as detailed above.
4. The fact that the compositions contains no water, or merely up to 5% and water minimizes the probability of degradation of water-sensitive active agents. Furthermore, as exemplified herein, a foam containing a polyol and/or PEG with no water at all can be formed in accordance with the composition and process of the present invention. Such compositions ensure high stability of water sensitive active agents.
5. Combining the anti-infective effect of a water-free, thus hygroscopic composition, which acts through a dehydration mechanism, with an additional anti-infective agent, selected from the group of an antibiotic agent, an antibacterial agent, an antifungal agent, an agent that controls yeast, an antiviral agent and an antiparasitic agent, that acts through alternate mechanisms results in a synergistic effect and consequently higher success rate of the treatment.
6. The foamable polyol composition in contained in an impermeable pressurized packaging presentation is impermeable and thus, the active agent is not exposed to environmental degradation factors, such as light and oxidating agent during storage.

Thus, in a preferred embodiment of the present invention, the composition includes at least one active agent.

- a. a therapeutically effective concentration of an active agent;
- b. a modulating agent;
- c. about 50% to about 98% of a polar solvent, selected from the group consisting of a polyol and a polyethylene glycol;
- d. 0% to about 48% of a secondary polar solvent;
- e. about 0.2% to about 5% by weight of a surface-active agent;

f. about 0.01% to about 5% by weight of at least one polymeric agent; and for a foamable composition additionally

g. a liquefied or compressed gas propellant at a concentration of about 3% to about 25% by weight of the total composition.

wherein the composition is stored in an aerosol container and upon release expands to form a breakable foam.

Active Agents

Suitable active agents include but are not limited to active herbal extracts, acaricides, age spot and keratose removing agents, allergen, analgesics, local anesthetics, antiacne agents, antiallergic agents, antiaging agents, antibacterials, antibiotics, antiburn agents, anticancer agents, antidandruff agents, antidepressants, antidermatitis agents, antiedemics, antihistamines, antihelminths, antihyperkeratolyte agents, antiinflammatory agents, antiirritants, antilipemics, antimicrobials, antimycotics, antiproliferative agents, antioxidants, anti-wrinkle agents, antipruritics, antipsoriatic agents, antirosacea agents antiseborrheic agents, antiseptic, antismelling agents, antiviral agents, antiyeast agents, astringents, topical cardiovascular agents, chemotherapeutic agents, corticosteroids, dicarboxylic acids, disinfectants, fungicides, hair growth regulators, hormones, hydroxy acids, immunosuppressants, immunoregulating agents, insecticides, insect repellents, keratolytic agents, lactams, metals, metal oxides, mitocides, neuropeptides, non-steroidal anti-inflammatory agents, oxidizing agents, pediculicides, photodynamic therapy agents, retinoids, sanatives, scabicides, self tanning agents, skin whitening agents, vasoconstrictors, vasodilators, vitamins, vitamin D derivatives, flavonoids, wound healing agents and wart removers. As is known to one skilled in the art, in some instances a specific active agent may have more than one activity, function or effect.

In an embodiment of the present invention, the active agent is an active herbal extract. Suitable active herbal extracts include but are not limited to angelica, anise oil, astragali radix, azalea, benzyl acetate, birch tar oil, bomyl acetate, cacumen biotae, camphor, cantharidin, capsicum, cineole, cinnamon bark, cinnamon leaf, citronella, citronellol, citronellyl acetate, citronellyl formate, eucalyptus, eugenyl acetate, flos carthami, fructus mori, garlic, geraniol, geranium, geranyl acetate, habanera, isobutyl angelicate, lavender, ledum latifolium, ledum palustre, lemongrass, limonene, linalool, linalyl acetate, methyl anthranilate, methyl cinnamate, mezezeum, neem, nerol, neryl acetate, nettle root extract, oleum ricini, oregano, pinenes, .alpha.-pinene, .beta.-pinene, radix angelicae sinesis, radix paenoiiae rubra, radix polygoni multiflori, radix rehmanniae, rhizoma pinelliae, rhizoma zingiberis recens, sabadilla, sage, sandalwood oil, saw palmetto extract, semen sesami nigrum, staphysagria, tea tree oil, terpene alcohols, terpene hydrocarbons, terpene esters, terpinene, terpineol, terpinyl acetate and derivatives, esters, salts and mixtures thereof. In an embodiment of the present invention, the active agent is an acaricide. Suitable acaricides include but are not limited to amitraz, flumethrin, fluralinate and derivatives, esters, salts and mixtures thereof.

In an embodiment of the present invention, the active agent is an age spot and keratoses removing agent. Suitable age spot and keratoses removing agent include but are not limited to hydroxy acids, azelaic acid and other related dicarboxylic acids, retinoids, kojic acid, arbutin, nicotinic, ascorbic acid, hydroquinone and derivatives, esters, salts and mixtures thereof. Certain nonsteroidal anti-inflammatory agents, such as diclofenac are also useful for the treatment of keratoses.

In an embodiment of the present invention, the active agent is an analgesic. Suitable analgesics include but are not limited

to benzocaine, butamben picrate, dibucaine, dimethisoquin, dyclonine, lidocaine, pramoxine, tetracaine, salicylates and derivatives, esters, salts and mixtures thereof.

In an embodiment of the present invention, the active agent is a local anesthetic. Suitable local anesthetics include but are not limited to benzocaine, benzyl alcohol, bupivacaine, butamben picrate, chlorprocaine, cocaine, dibucaine, dimethisoquin, dyclonine, etidocaine, hexylcaine, ketamine, lidocaine, mepivacaine, phenol, pramoxine, procaine, tetracaine, salicylates and derivatives, esters, salts and mixtures thereof.

In an embodiment of the present invention, the active agent is an antiacne agent. Suitable antiacne agents include but are not limited to N-acetylcysteine, adapalene, azelaic acid, benzoyl peroxide, cholate, clindamycin, deoxycholate, erythromycin, flavinoids, glycolic acid, meclocycline, metronidazole, mupirocin, octopirox, phenoxy ethanol, phenoxy propanol, pyruvic acid, resorcinol, retinoic acid, salicylic acid, scymnol sulfate, sulfacetamide-sulfur, sulfur, tazarotene, tetracycline, tretinoin triclosan and derivatives, esters, salts and mixtures thereof.

In an embodiment of the present invention, the active agent is an antiaging agent. Suitable antiaging agents include but are not limited to sulfur-containing D and L amino acids, alpha-hydroxy acids, beta-hydroxy acids (e.g. salicylic acid), urea, hyaluronic acid, phytic acid, lipoic acid; lysophosphatidic acid, skin peel agents (e.g., phenol, resorcinol and the like), vitamin B3 compounds (e.g., niacinamide, nicotinic acid and nicotinic acid salts and esters, including non-vasodilating esters of nicotinic acid (such as tocopheryl nicotinate), nicotinyl amino acids, nicotinyl alcohol esters of carboxylic acids, nicotinic acid N-oxide and niacinamide N-oxide), vitamin B5 and retinoids (e.g., retinol, retinal, retinoic acid, retinyl acetate, retinyl palmitate, retinyl ascorbate) skin barrier forming agents, melatonin and derivatives, esters, salts and mixtures thereof.

In an embodiment of the present invention, the active agent is an antibiotic. The terms "antibiotic" as used herein shall include, but is not limited to, any substance being destructive to or inhibiting the growth of bacteria or any substance having the capacity to inhibit the growth of or to destroy bacteria. In one or more embodiments, the antibiotic agent is selected from the group consisting of a beta-lactam antibiotic, an aminoglycoside, an ansa-type antibiotic, an anthraquinone, an azole, an antibiotic glycopeptide, a macrolide, an antibiotic nucleoside, an antibiotic peptide, an antibiotic polyene, an antibiotic polyether, an antibiotic quinolone, an antibiotic steroid, a sulfonamide, an antibiotic metal, an oxidizing agent, a periodate, a hypochlorite, a permanganate, a substance that release free radicals and/or active oxygen, a cationic antimicrobial agent, a quaternary ammonium compound, a biguanide, a triguanide, a bisbiguanide, a polymeric biguanide, and analogs, derivatives, salts, ions and complexes thereof.

Suitable antibiotics include but are not limited to amfanidine hydrochloride, amfanidine sulfate, amikacin, amikacin sulfate, aminoglycosides, amoxicillin, ampicillin, ansamycins, bacitracin, beta-lactams, candididin, capreomycin, carbenicillin, cephalixin, cephaloridine, cephalothin, cefazolin, cepiparin, cephradine, cephaloglycin, chloramphenicols, chlorhexidine, chlorhexidine gluconate, chlorhexidine hydrochloride, chloroxine, chlorquinaldol, chlortetracycline, chlortetracycline hydrochloride, ciprofloxacin, circulin, clindamycin, clindamycin hydrochloride, clotrimazole, cloxacillin, demeclocycline, diclosxacillin, diiodohydroxyquin, doxycycline, ethambutol, ethambutol hydrochloride, erythromycin, erythromycin estolate, erythromycin stearate, far-

nesol, floxacillin, gentamicin, gentamicin sulfate, gramacidin, griseofulvin, haloprogin, haloquinol, hexachlorophene, iminocyclidine, iodate, iodine, iodochlorhydroxyquin, kanamycin, kanamycin sulfate, lincomycin, lineomycin, lineomycin hydrochloride, macrolides, meclocycline, methacycline, methacycline hydrochloride, methenamine, methenamine hippurate, methenamine mandelate, methicillin, metronidazole, miconazole, miconazole hydrochloride, microcrystalline and nanocrystalline particles of silver, copper, zinc, mercury, tin, lead, bismuth, cadmium and chromium, minocycline, minocycline hydrochloride, mupirocin, nafcillin, neomycin, neomycin sulfate, netilmicin, netilmicin sulfate, nitrofurazone, norfloxacin, nystatin, octopirox, oleandomycin, orcephalosporins, oxacillin, oxytetracycline, oxytetracycline hydrochloride, parachlorometa xylenol, paromomycin, paromomycin sulfate, penicillins, penicillin G, penicillin V, pentamidine, pentamidine hydrochloride, phenethicillin, polymyxins, quinolones, streptomycin sulfate, tetracycline, tobramycin, tolnaftate, triclosan, trifampin, rifamycin, rolitetracycline, spectinomycin, spiramycin, streptomycin, sulfonamide, tetracyclines, tetracycline, tobramycin, tobramycin sulfate, triclocarbon, triclosan, trimethoprim-sulfamethoxazole, tylosin, vancomycin, yrothricin and derivatives, esters, salts and mixtures thereof.

In an embodiment of the present invention, the active agent is an antidandruff agent. Suitable antidandruff agents include but are not limited to aminexil, benzalkonium chloride, benzethonium chloride, 3-bromo-1-chloro-5,5-dimethylhydantoin, chloramine B, chloramine T, chlorhexidine, N-chlorosuccinimide, climbazole-, 1,3-dibromo-5,5-dimethylhydantoin, 1,3-dichloro-5,5-dimethylhydantoin, betulonic acid, betulonic acid, celastrol, crataegolic acid, cromakalin, cyproterone acetate, dutasteride, finasteride, ibuprofen, ketoconazole, oleanolic acid, phenytoin, picrotone olamine, salicylic acid, selenium sulphides, triclosan, triiodothyronine, ursolic acid, zinc gluconate, zinc omadine, zinc pyrithione and derivatives, esters, salts and mixtures thereof.

In an embodiment of the present invention, the active agent is an antihistamine. Suitable antihistamines include but are not limited to chlorcyclizine, diphenhydramine, mepyramine, methapyrilene, tripeleminamine and derivatives, esters, salts and mixtures thereof.

In an embodiment of the present invention, the active agent is an antimycotic. Also termed antifungal agent. The terms "antimycotic" and "antifungal" as used herein include, but is not limited to, any substance being destructive to or inhibiting the growth of fungi and yeast or any substance having the capacity to inhibit the growth of or to destroy fungi and/or yeast.

In one or more embodiments, the antifungal agent is an agent that is useful in the treatment of a superficial fungal infection of the skin, dermatophytosis, microsporum, trichophyton and epidermophyton infections, candidiasis, oral candidiasis (thrush), candidiasis of the skin and genital mucous membrane, candida paronychia, which inflicts the nail and nail bed and genital and vaginal candida, which inflict genitalia and the vagina.

Suitable antimycotics include but are not limited to allylamines, amorolfine, amphotericin B, azole compounds, bifonazole, butoconazole, chloroxine, clotrimazole, ciclopirox olamine, clotrimazole, econazole, elubiol, fenticonazole, fluconazole, flucytosine (5FC), griseofulvin, itraconazole, ketoconazole, mafenide acetate, miconazole, naftifine, natamycin, tolnaftate, nystatin, polyenes, oxiconazole, sul-

bentine, sulconazole, terbinafine, terconazole, tioconazole, undecylenic acid and derivatives, esters, salts and mixtures thereof.

In an embodiment of the present invention, the active agent is an antipruritic. Suitable antipruritics include but are not limited to menthol, methdilazine, trimeprazine, urea and derivatives, esters, salts and mixtures thereof.

In an embodiment of the present invention, the active agent is an additional antipsoriatic agent. Suitable additional antipsoriatic agents include but are not limited to 6-aminonicotinamide, 6-aminonicotinic acid, 2-aminopyrazinamide, anthralin, 6-carbamoylnicotinamide, 6-chloronicotinamide, 2-carbamoylpyrazinamide, corticosteroids, 6-dimethylaminonicotinamide, dithranol, 6-formylaminonicotinamide, 6-hydroxy nicotinic acid, 6-substituted nicotinamides, 6-substituted nicotinic acid, 2-substituted pyrazinamide, tazarotene, thionicotinamide, trichothecene mycotoxins and derivatives, esters, salts and mixtures thereof.

In an embodiment of the present invention, the active agent is an antirosacea agent. Suitable antirosacea agents include but are not limited to azelaic acid, metronidazole, sulfacetamide and derivatives, esters, salts and mixtures thereof. Certain nonsteroidal anti-inflammatory agents, such as salicylic acid, salicylates, piroxicam and diclofenac are also useful for the treatment of Rosacea.

In an embodiment of the present invention, the active agent is an antiseborrheic agent. Suitable antiseborrheic agents include but are not limited to glycolic acid, salicylic acid, selenium sulfide, zinc pyrithione, a dicarboxylic acid, such as azelaic acid and derivatives, esters, salts and mixtures thereof.

In an embodiment of the present invention, the active agent is an antiviral agent. Suitable antiviral agents include but are not limited to acyclovir, gancyclovir, ribavirin, amantadine, rimantadine nucleoside-analog reverse transcriptase inhibitors, such as zidovudine, didanosine, zalcitabine, stavudine, lamivudine and vidarabine, non-nucleoside reverse transcriptase inhibitors, such as nevirapine and delavirdine, protease inhibitors, such as saquinavir, ritonavir, indinavir and nelfinavir, and interferons and derivatives, esters, salts and mixtures thereof.

In an embodiment of the present invention, the active agent is a chemotherapeutic agent. Suitable chemotherapeutic agents include but are not limited to daunorubicin, doxorubicin, idarubicin, amrubicin, pirarubicin, epirubicin, mitoxantrone, etoposide, teniposide, vinblastine, vincristine, mitomycin C, 5-FU, paclitaxel, docetaxel, actinomycin D, colchicine, topotecan, irinotecan, gemcitabine cyclosporin, verapamil, valsopodol, probenecid, MK571, GF120918, LY335979, biricodar, terfenadine, quinidine, pervilleine A, XR9576 and derivatives, esters, salts and mixtures thereof.

In an embodiment of the present invention, the active agent is a corticosteroid. Suitable corticosteroids include but are not limited to alclometasone dipropionate, amcinafel, amcinafide, amcinonide, beclomethasone, beclomethasone dipropionate, betamethasone, betamethasone benzoate, betamethasone dexamethasone-phosphate, dipropionate, betamethasone valerate, budesonide, chloroprednisone, chlorprednisone acetate, clescinolone, clobetasol, clobetasol propionate, clobetasol valerate, clobetasone, clobetasone butyrate, clocortelone, cortisone, cortodoxone, crapsone butyrate, desonide, desoxymethasone, dexamethasone, desoxycorticosterone acetate, dichlorisone, diflorasone diacetate, diflucortolone valerate, diflurosone diacetate, difluprednate, fludrenolone, flucetonide, flucoronide, flucorolone acetonide, flucortine butylesters, fludroxycortide, fludrocortisone, flumethasone, flumethasone pivalate, flumethasone pivalate, flunisolide, fluocinolone, fluo-

cinolone acetonide, fluocinonide, fluocortin butyl, fluocortolone, fluorometholone, fluosinolone acetonide, fluperalone, fluprednidene acetate, fluprednisolone hydrocortamate, fluradrenolone, fluradrenolone acetonide, flurandrenolone, fluticasone, halcinonide, halobetasol, hydrocortisone, hydrocortisone acetate, hydrocortisone butyrate, hydrocortisone cyclopentylpropionate, hydrocortisone valerate, hydroxyltriamcinolone, medrysone, meprednisone, .alpha.-methyl dexamethasone, methylprednisolone, methylprednisolone acetate, mometasone furoate, paramethasone, prednisolone, prednisone, pregnenolone, progesterone, spironolactone, triamcinolone, triamcinolone acetonide and derivatives, esters, salts and mixtures thereof.

In an embodiment of the present invention, the active agent is a hair growth regulator. Suitable hair growth regulators include but are not limited to N-acetylglucosamine, N-acetylglucosamine, N-acetylmannosamine, acitretin, aminexil, ascomycin, asiatic acid, azelaic acid, benzalkonium chloride, benzethonium chloride, benzydamine, benzyl nicotine, benzoyl peroxide, benzyl peroxide, betulinic acid, betulonic acid, calcium pantothenate, celestrol, cepharanthine, chlorpheniramine maleate, clinacyn hydrochloride, crataegolic acid, cromakalin, cyproterone acetate, diazoxide, diphenhydramine hydrochloride, dutasteride, estradiol, ethyl-2-hydroxypropanoate, finasteride, D-fucono-1,5-lactone, furoate, L-galactono-1,4-lactone, D-galactosamine, D-glucaro-1,4-lactone, D-glucosamine-3-sulphate, hinokitiol, hydrocortisone, 2-hydroxypropionic acid, isotretinoin, itraconazole, ketoconazole, latanoprost, 2-methyl propan-2-ol, minocyclin, minoxidil, mipirocin, mometasone, oleanolic acid, panthenol, 1,10-phenanthroline, phenytoin, prednisolone, progesterone, propan-2-ol, pseudoterins, resorcinol, selenium sulfide, tazarotene, triclocarbon, triclosan, triiodothyronine, ursolic acid, zinc pyrithione and derivatives, esters, salts and mixtures thereof.

In an embodiment of the present invention, the active agent is a hormone. Suitable hormones include but are not limited to methyltestosterone, androsterone, androsterone acetate, androsterone propionate, androsterone benzoate, androsteronediol, androsteronediol-3-acetate, androsteronediol-17-acetate, androsteronediol 3-17-diacetate, androsteronediol-17-benzoate, androsteronedione, androstenedione, androstenediol, dehydroepiandrosterone, sodium dehydroepiandrosterone sulfate, dromostanolone, dromostanolone propionate, ethylestrenol, fluoxymesterone, nandrolone phenpropionate, nandrolone decanoate, nandrolone furoylpropionate, nandrolone cyclohexane-propionate, nandrolone benzoate, nandrolone cyclohexanecarboxylate, androsteronediol-3-acetate-1-7-benzoate, oxandrolone, oxymetholone, stanozolol, testosterone, testosterone decanoate, 4-dihydrotestosterone, 5a-dihydrotestosterone, testolactone, 17a-methyl-19-nortestosterone, desogestrel, dydrogesterone, ethynodiol diacetate, medroxyprogesterone, levonorgestrel, medroxyprogesterone acetate, hydroxyprogesterone caproate, norethindrone, norethindrone acetate, norethynodrel, allylestrenol, 19-nortestosterone, linoestrenol, quingestanol acetate, medrogestone, norgestrienone, dimethisterone, ethisterone, cyproterone acetate, chlormadinone acetate, megestrol acetate, norgestimate, norgestrel, desogestrel, trimegestone, gestodene, nomegestrol acetate, progesterone, 5a-pregnan-3b,20a-diol sulfate, 5a-pregnan-3b,20b-diol sulfate, 5a-pregnan-3b-ol-20-one, 16,5a-pregnen-3b-ol-20-one, 4-pregnen-20b-ol-3-one-20-sulfate, acetoxyprogesterone, anagestone acetate, cyproterone, dihydrogesterone, flurogestone acetate, gestadene, hydroxyprogesterone acetate, hydroxymethylprogesterone, hydroxymethyl progesterone acetate, 3-ketodesogestrel,

megestrol, melengestrol acetate, norethisterone, progestins and derivatives, esters, salts and mixtures thereof.

In an embodiment of the present invention, the active agent is a hydroxyacid. Suitable hydroxy acids include but are not limited to agaricic acid, aleuritic acid, allaric acid, altraric acid, arabiraric acid, ascorbic acid, atrolactic acid, benzilic acid, citramalic acid, citric acid, dihydroxytartaric acid, erythraric acid, galactaric acid, galacturonic acid, glucaric acid, glucuronic acid, glyceric acid, glycolic acid, gularic acid, gulonic acid, hydroxypyruvic acid, idaric acid, isocitric acid, lactic acid, lyxaric acid, malic acid, mandelic acid, mannaric acid, methylactic acid, mucic acid, phenyllactic acid, pyruvic acid, quinic acid, ribaric acid, ribonic acid, saccharic acid, talaric acid, tartaric acid, tartronic acid, thearic acid, tropic acid, uronic acids, xylaric acid and derivatives, esters, salts and mixtures thereof.

In an embodiment of the present invention, the active agent is a keratolytic agent. The term "keratolytic agent" is used herein to mean a compound which loosens and removes the stratum corneum of the skin, or alters the structure of the keratin layers of skin. Keratolytic agents are used in the treatment of many dermatological disorders, which involve dry skin, hyperkeratinization (such as psoriasis), skin itching (such as xerosis), acne and rosacea. Suitable keratolytic agents include but are not limited to N-acetylcysteine, azelaic acid, cresols, dihydroxy benzene compounds, such as resorcinol and hydroquinone, alpha-hydroxy acids, such as lactic acid and glycolic acid, phenol, pyruvic acid, resorcinol, sulfur, salicylic acid, retinoic acid, isotretinoic acid, retinol, retinal, urea and derivatives, esters, salts and mixtures thereof.

In an embodiment of the present invention, the active agent is a lactam. Suitable lactams include but are not limited to L-galactono-1,4-lactam, L-arabino-1,5-lactam, D-fucono-1,5-lactam, D-glucaro-1,4-lactam, D-glucurono-6,3-lactam, 2,5-tri-O-acetyl-D-glucurono-6,3-lactam, 2-acetamido-2-deoxyglucano-1,5-lactam, 2-acetamido-2-deoxygalactono-1,5-lactam, D-glucaro-1,4:6,3-dilactam-, L-idaro-1,5-lactam, 2,3,5-tri-O-acetyl-D-glucaro-1,4-lactam, 2,5-di-O-acetyl-D-glucaro-1,4:6,3-dilactam, D-glucaro-1,5-lactam methyl ester, 2-propionamide-2-deoxyglucaro-1,5-lactam and derivatives, esters, salts and mixtures thereof.

In an embodiment of the present invention, the active agent is a non-steroidal anti-inflammatory agent. Suitable non-steroidal anti-inflammatory agent include but are not limited to azelaic acid, oxicams, piroxicam, isoxicam, tenoxicam, sudoxicam, CP-14,304, salicylates, aspirin, disalicyl, benorylate, trilisate, safapryn, solprin, diflunisal, fendosal, acetic acid derivatives, diclofenac, fenclofenac, indomethacin, sulindac, tolmetin, isoxepac, furofenac, tiopinac, zidometacin, acematacin, fentiazac, zomepirac, clindanac, oxepinac, felbinac, ketorolac, fenamates, mefenamic, meclofenamic, flufenamic, niflumic, tolfeamic acids, propionic acid derivatives, ibuprofen, naproxen, benoxaprofen, flurbiprofen, ketoprofen, fenoprofen, fenbufen, indoprofen, piroprofen, carprofen, oxaprozin, pranoprofen, miroprofen, tioxaprofen, suprofen, alminoprofen, tiaprofen, pyrazoles, phenylbutazone, oxyphenbutazone, feprazone, azapropazone, trimethazone and derivatives, esters, salts and mixtures thereof.

In an embodiment of the present invention, the active agent is insecticide. The term "insecticide" is used herein to mean a compound which kills, inhibits the growth of, impedes the proliferation of or repels insects. Insecticides include, for example, agents that can kill lice, flees, ticks, mites, scabies and mosquitos, as well as agents that repel such insects. Suitable insecticides include but are not limited to DDT, lindane, malathion, permethrin, allethrin, biopermethrin, transpermethrin, phenothrin, diethyl-m-toluamide, dimethyl

phthalate, piperonyl butoxide, pyrethroids and derivatives, esters, salts and mixtures thereof.

In an embodiment of the present invention, the active agent is a vasodilator. Suitable vasodilators include but are not limited to agents that modulate the activity of the enzyme nitric oxide synthase, nicotinic acid, ethyl nicotinate, amyl nitrite, amyl nitrate, ethyl nitrite, butyl nitrite, isobutyl nitrite, glyceryl trinitrate, octyl nitrite, sodium nitrite, sodium nitroprusside, clonitrate, erythrityl tetranitrate, isosorbide mononitrate, isosorbide dinitrate, mannitol hexanitrate, pentaerythritol tetranitrate, penetrinitol, triethanolamine trinitrate, trinitrate phosphate (triethanolamine trinitrate diphosphate), propatynitrate, nitrite esters of sugars, nitrite esters of polyols, nitrate esters of sugars, nitrate esters of polyols, nicorandil, apresoline, diazoxide, hydralazine, hydrochlorothiazide, minoxidil, pentaerythritol, tolazoline, scoparone, a beta-adrenergic blocker, an alpha-adrenoceptor blocker, a prostaglandin, sildenafil, dipyrindamole, catecholamine, isoproterenol, furosemide, prostaglandin, prostacyclin, enalaprilat, morphine, acepromazine, prazosin (α -blocker), enalapril, Captopril, amlodipine, minoxidil, tadalafil, vardenafil, phenylephrin, etilefein, caffeine, capsaicin, an extract *capsicum*, *achillea millefolium* (Yarrow), *allium sativum* (garlic), *amoracia rusticana* (horseradish), *berberis vulgaris* (barberry), *cimicifuga racemosa* (black cohosh), *coleus forskohlii* (coleus), *coptis* (goldenthread), *crataegus* (hawthorn), *eleutherococcus senticosus* (siberian ginseng), *ginkgo biloba* (ginkgo), *melissa officinalis* (lemon balm), *olea europaea* (olive leaf), *panax ginseng* (Chinese ginseng), *petroselinum crispum* (parsley), *scutellaria baicalensis* (baical skullcap), *tilia europaea* (linden flower), *trigonella foenum-graecum* (fenugreek), *urtica dioica* (nettles), *valeriana officinalis* (valerian), *viburnum* (cramp, bark, black haw), *veratrum viride* (American hellebore), *verbena officinalis* (vervain), *xanthoxylum americanum* (prickly ash), *zingiber officinale* (ginger), *rauwolfia serpentina* (Indian snakeroot), *viscum album*, wild yam, sasparilla, licorice, damiana, yucca, saw palmetto, gotu kola (*centella asiatica*), yohimbine and salts, hazel nut, brazil nut and walnut, and derivatives, esters, salts and mixtures thereof.

In an embodiment of the present invention, the active agent is a vasoconstrictor. Suitable vasodilators include but are not limited to ephedrine, epinephrine, phenylephrine, angiotensin, vasopressin; an extract *ephedra sinica* (ma huang), *polygonum bistorta* (bistort root), *hamamelis virginiana* (witch hazel), *hydrastis canadensis* (goldenseal), *lycopus virginicus* (bugleweed), *aspidosperma quebracho* (*quebracho blanco*), *cytissus scoparius* (scotch broom) and cypressand and derivatives, esters, salts and mixtures thereof.

In an embodiment of the present invention, the active agent is a retinoid. Suitable retinoids include but are not limited to retinol, retinal, retinoic acid, all-trans retinoic acid, isotretinoin, tazarotene, adapalene, 13-cis-retinoic acid, acitretin all-trans beta carotene, alpha carotene, lycopene, 9-cis-beta-carotene, lutein and zeaxanthin.

In an embodiment of the present invention, the active agent is a vitamin D analog. Suitable retinoids include but are not limited to calcipotriene, cholecalciferol, 25-hydroxycholecalciferol, 1 α ,25-dihydroxycholecalciferol, ergocalciferol, 1 α ,25-dihydroxyergocalciferol, 22,23-dihydroergocalciferol, 1,24,25-trihydroxycholecalciferol, previtamin D₃, tachysterol₃ (also termed tacalcinol), isovitamin D₃, dihydrotachysterol₃, (1S)-hydroxycalcinol, (24R)-hydroxycalcidiol, 25-fluorocalciol, ercalcidiol, ertacalcinol, (5E)-isocalciol, 22,23-dihydroercalcinol, (24S)-methylcalciol, (5E)-(10S)-10, 19-dihydroercalcinol, (24S)-ethylcalciol and (22E)-(24R)-

ethyl-22,23-didehydrocalciol. In a preferred embodiment, the vitamin D analog is calcipotriene, which is useful in the treatment of psoriasis.

In an embodiment of the present invention, the active agent is selected from the group consisting of an immunosuppressant and immunoregulating agents. Suitable immunosuppressants and immunoregulating agents include but are not limited to cyclic peptides, such as cyclosporine, tacrolimus, tresperimus, pimecrolimus, sirolimus (rapamycin), verolimus, laflunimus, laquinimod, imiquimod derivatives, esters, salts and mixtures thereof. In one or more embodiments, the immunomodulator is a calcineurin Inhibitor.

In an embodiment of the present invention, the active agent is a wart remover. Suitable wart removers include but are not limited to imiquimod, podophyllotoxin and derivatives, esters, salts and mixtures thereof.

In an embodiment of the present invention, the active agent is a photodynamic therapy (PDT) agent. Suitable PDT agents include but are not limited to modified porphyrins, chlorins, bacteriochlorins, phthalocyanines, naphthalocyanines, pheophorbides, purpurins, m-THPC, mono-L-aspartyl chlorin e6, bacteriochlorins, phthalocyanines, benzoporphyrin derivatives, as well as photosensitizer precursors, such as aminolevulinic acid and derivatives, esters, salts and mixtures thereof.

In an embodiment of the present invention, the active agent is an antioxidant or a radical scavenger. Suitable antioxidants and radical scavengers agents include but are not limited to ascorbic acid, ascorbyl esters of fatty acids, magnesium ascorbyl phosphate, sodium ascorbyl phosphate, ascorbyl sorbate, tocopherol, tocopheryl sorbate, tocopheryl acetate, butylated hydroxy benzoic acid, 6-hydroxy-2,5,7,8-tetramethylchroman-2-carboxylic acid, gallic acid, propyl gallate, uric acid, sorbic acid, lipoic acid, diethylhydroxylamine, amino-guanidine, glutathione, dihydroxy fumaric acid, lycine pidolate, arginine pilolate, nordihydroguaiaretic acid, bioflavonoids, curcumin, lysine, methionine, proline, superoxide dismutase, silymarin, tea extracts, grape skin/seed extracts, melanin, and polyunsaturated oils, containing omega-3 and omega-6 fatty acids (e.g., linoleic and linolenic acid, gamma-linolenic acid, eicosapentaenoic acid and docosahexaenoic acid and derivatives, esters, salts and mixtures thereof).

In an embodiment of the present invention, the active agent is a self-tanning agent, such as dihydroxyacetone.

In an embodiment of the present invention, the active agent is an agent, capable of treating hyperhidrosis. Suitable hyperhidrosis agents include but are not limited to anticholinergic drugs, boric acid, tannic acid, resorcinol, potassium permanganate, formaldehyde, glutaraldehyde, methenamine, a Lewis acid, aluminum chloride, aluminum chlorohydrates, zirconium chlorohydrates, aluminum-zirconium-Glycine (AZG) complex, aluminum hydroxybromide, a glycopyrrolate compound, a 5-alpha-reductase inhibitor, finasteride, epristeride, flutamide, spironolactone, saw palmetto extract, cholestan-3-one, a mono- and dicarboxylic acid having 4 to 18 carbon atoms, botulinum toxin, a 5-HT_{2C} receptor antagonist, a 5-HT_{2C} receptor antagonist, ketanserine, ritanserine, mianserine, mesulergine, cyproheptadine, fluoxetine, mirtazapine, olanzapine and ziprasidone.

In an embodiment of the present invention, the active agent is a sunscreen agent. Suitable sunscreen agents include but are not limited to titanium dioxide, zinc oxide, zirconium oxide, iron oxide, p-aminobenzoic acid and its derivatives (ethyl, isobutyl, glyceryl esters; p-dimethylaminobenzoic acid); anthranilic acid derivatives (i.e., o-amino-benzoates, methyl, menthyl, phenyl, benzyl, phenylethyl, linalyl, terpi-

nyl, and cyclohexenyl esters); salicylates (amyl, phenyl, octyl, benzyl, menthyl, glyceryl, and di-pro-pyleneglycol esters); cinnamic acid derivatives (menthyl and benzyl esters, a-phenyl cinnamoyl pyruvate); butyl cinnamoyl pyruvate); dihydroxycinnamic acid derivatives (umbelliferone, methylumbelliferone, methylaceto-umbelliferone); trihydroxy-cinnamic acid derivatives (esculetin, methylesculetin, daphnetin, and the glucosides, esculin and daphnin); hydrocarbons (diphenylbutadiene, stilbene); dibenzalacetone and benzalacetophenone; naphtholsulfonates (sodium salts of 2-naphthol-3,6-disulfonic and of 2-naphthol-6,8-disulfonic acids); di-hydroxynaphthoic acid, o- and p-hydroxybiphenyldisulfonates, coumarin derivatives (7-hydroxy, 7-methyl, 3-phenyl), diazoles (2-acetyl-3-bromindazole, phenyl benzoxazole, methyl naphthoxazole, quinine salts (bisulfate, sulfate, chloride, oleate, and tannate); quinoline derivatives (8-hydroxyquinoline salts, 2-phenylquinoline); hydroxy- or methoxy-substituted benzophenones; uric and violuric acids; tannic acid and its derivatives (e.g., hexaethylether); (butyl carbonyl) (6-propyl piperonyl) ether; hydroquinone; benzophenones (oxybenzene, sulisobenzene, dioxybenzene, benzoresorcinol, 2,2',4,4'-tetrahydroxybenzophenone, 2,2'-dihydroxy-4,4'-dimethoxybenzophenone, octabenzene; 4-isopropylidibenzoylmethane; butylmethoxydibenzoylmethane; etocrylene; octocrylene; [3-(4'-methylbenzylidene bornan-2-one), terephthalylidene dicamphor sulfonic acid and 4-isopropyl-di-benzoylmethane.

In an embodiment of the present invention, the active agent is a figure-forming agent and an agent, capable of treating cellulite. Suitable such agents include but are not limited to balderwack extract, butcher's, broom, cayenne, dandelion, red clover, *ginkgo biloba*, horse chestnut, witch hazel and borage oil, caffeic acid, nicotinic acid, theophylline and pentoxifylline and salts and derivatives thereof.

Several disorders of the skin, body cavity or mucosal surface (e.g., the mucosa or the cavity of the nose, mouth, eye, ear, vagina or rectum) involve a combination of etiological factors. For example, fungal and bacterial infections and that are inflamed and have symptoms of redness and/or itching warrant therapy that combines an anti-infective agent and an anti-inflammatory agent. Thus, in several cases, combining at least two active agents that treat different etiological factors results in a synergistic effect and consequently higher success rate of the treatment.

In certain cases, the composition contains two active agents, where each of the active agents require a different pH environment in order to remain stable. For example, corticosteroids are typically stable at acidic pH values (they have a maximum stability at a pH of about 4-6) and of vitamin D analogues are typically stable at basic pH values (they have a maximum stability at pH values above about 8). In order to circumvent the problem of instability it is preferred that the composition is substantially non-aqueous or preferably waterless. The term "substantially non-aqueous" is intended to indicate that the composition has a water content below about 5%, preferably below about 2%, such as below about 1.5%. The formulation can then be modulated by a modulating agent additive that provides, for example, an artificial pH closer to the more sensitive of the two sensitive actives or alternatively closer to the more pH sensitive of the two actives. On a pragmatic level formulating the composition with an artificial pH close to that of skin may be an advantage.

In one or more embodiments the active pharmaceutical or cosmetic agent is an agent which is sensitive to pH such that it is more stable at a certain pH or pH range and tends to react or break down or isomerise at a different pH or pH range. In a preferred embodiment the active agent includes the follow-

ing non limiting examples: steroids (most are stable at acidic ph of about 4.5); antibiotics, such as tetracycline's which are stable at acidic ph (e.g. oxytetracycline, clindamycin); penicillinic and cephalosporinic antibiotics, (such as, ampicillin, benzylpenicillin, carbenicillin, cephadroxil, cefotaxime, cephalotin, and cephradine); triamcinolone; nystatin (stable at about ph 7.0); sulfacetamide; and amphotericin; vitamins are generally ph sensitive and examples are ascorbic acid which is stable in slightly acidic conditions and vitamin D analogues that are stable at basic pH, and nicotine amide; NSAID's such as aspirin and indomethacin; atropine; pilocarpine; procaine amide; aztreonam; barbiturates; captopril nucleotide derivatives such as cytarabineepinephrine; parabens such as ethylparaben methylparaben; anticancer agents such as fluorouracil and iodoxuridine; morphine analgesic; prostaglandins and thiamine HCl.

Fields of Applications

The foamable carrier of the present invention is suitable for treating any infected surface. In one or more embodiments, foamable carrier is suitable for administration to the skin, a body surface, a body cavity or mucosal surface, e.g., the cavity and/or the mucosa of the nose, mouth, eye, ear, respiratory system, vagina or rectum (severally and interchangeably termed herein "target site").

By selecting a suitable active agent, or a combination of at least two active agents, the foamable composition of the present invention is useful in treating an animal or a human patient having any one of a variety of dermatological disorders, including dermatological pain, dermatological inflammation, acne, acne vulgaris, inflammatory acne, non-inflammatory acne, acne fulminans, nodular papulopustular acne, acne conglobata, dermatitis, bacterial skin infections, fungal skin infections, viral skin infections, parasitic skin infections, skin neoplasia, skin neoplasms, pruritis, cellulitis, acute lymphangitis, lymphadenitis, erysipelas, cutaneous abscesses, necrotizing subcutaneous infections, scalded skin syndrome, folliculitis, furuncles, hidradenitis suppurativa, carbuncles, paronychia infections, rashes, erythrasma, impetigo, ecthyma, yeast skin infections, warts, molluscum contagiosum, trauma or injury to the skin, post-operative or post-surgical skin conditions, scabies, pediculosis, creeping eruption, eczemas, psoriasis, pityriasis rosea, lichen planus, pityriasis rubra pilaris, edematous, erythema multiforme, erythema nodosum, granuloma annulare, epidermal necrolysis, sunburn, photosensitivity, pemphigus, bullous pemphigoid, dermatitis herpetiformis, keratosis pilaris, callosities, corns, ichthyosis, skin ulcers, ischemic necrosis, miliaria, hyperhidrosis, moles, Kaposi's sarcoma, melanoma, malignant melanoma, basal cell carcinoma, squamous cell carcinoma, poison ivy, poison oak, contact dermatitis, atopic dermatitis, rosacea, purpura, moniliasis, candidiasis, baldness, alopecia, Behcet's syndrome, cholesteatoma, Dercum disease, ectodermal dysplasia, gustatory sweating, nail patella syndrome, lupus, hives, hair loss, Hailey-Hailey disease, chemical or thermal skin burns, scleroderma, aging skin, wrinkles, sun spots, necrotizing fasciitis, necrotizing myositis, gangrene, scarring, and vitiligo.

Likewise, the foamable composition of the present invention is suitable for treating a disorder of a body cavity or mucosal surface, e.g., the mucosa of the nose, mouth, eye, ear, respiratory system, vagina or rectum. Non limiting examples of such conditions include chlamydia infection, gonorrhea infection, hepatitis B, herpes, HIV/AIDS, human papillomavirus (HPV), genital warts, bacterial vaginosis, candidiasis, chancroid, granuloma Inguinale, lymphogranuloma venereum, mucopurulent cervicitis (MPC), molluscum contagiosum, nongonococcal urethritis (NGU), trichomoniasis,

vulvar disorders, vulvodynia, vulvar pain, yeast infection, vulvar dystrophy, vulvar intraepithelial neoplasia (VIN), contact dermatitis, pelvic inflammation, endometritis, salpingitis, oophoritis, genital cancer, cancer of the cervix, cancer of the vulva, cancer of the vagina, vaginal dryness, dyspareunia, anal and rectal disease, anal abscess/fistula, anal cancer, anal fissure, anal warts, Crohn's disease, hemorrhoids, anal itch, pruritus ani, fecal incontinence, constipation, polyps of the colon and rectum.

In an embodiment of the present invention, the composition is useful for the treatment of an infection. In one or more embodiments, the composition is suitable for the treatment of an infection, selected from the group of a bacterial infection, a fungal infection, a yeast infection, a viral infection and a parasitic infection.

In an embodiment of the present invention, the composition is useful for the treatment of wound, ulcer and burn. This use is particularly important since the composition of the present invention creates a thin, semi-occlusive layer, which coats the damaged tissue, while allowing exudates to be released from the tissue.

The composition of the present invention is also suitable for administering a hormone to the skin or to a mucosal membrane or to a body cavity, in order to deliver the hormone into the tissue of the target organ, in any disorder that responds to treatment with a hormone.

In light of the hygroscopic nature of the water-free composition, it is further suitable for the treatment and prevention of post-surgical adhesions. Adhesions are scars that form abnormal connections between tissue surfaces. Post-surgical adhesion formation is a natural consequence of surgery, resulting when tissue repairs itself following incision, cauterization, suturing, or other means of trauma. When comprising appropriate protective agents, the foam is suitable for the treatment or prevention of post surgical adhesions. The use of foam is particularly advantageous because foam can expand in the body cavity and penetrate into hidden areas that cannot be reached by any other alternative means of administration. Substantially Alcohol-Free

According to one or more embodiments, the foamable composition is substantially alcohol-free, i.e., free of short chain alcohols. Short chain alcohols, having up to 5 carbon atoms in their carbon chain skeleton and one hydroxyl group, such as ethanol, propanol, isopropanol, butaneol, iso-butaneol, t-butaneol and pentanol, are considered less desirable solvents or polar solvents due to their skin-irritating effect. Thus, the composition is substantially alcohol-free and includes less than about 5% final concentration of lower alcohols, preferably less than about 2%, more preferably less than about 1%.

Shakability

'Shakability' means that the composition contains some or sufficient flow to allow the composition to be mixed or remixed on shaking. That is, it has fluid or semi fluid properties. In some very limited cases it may still be possible to have a foamable composition which is flowable but not apparently shakable.

Breakability

A breakable foam is thermally stable or substantially so, yet breaks under sheer force. The breakable foam of the present invention is not "quick breaking", i.e., it does not readily collapse upon exposure to body temperature environment. Sheer-force breakability of the foam is clearly advantageous over thermally induced breakability, (due to, for example, the presence of alcohol) since it allows comfortable application and well directed administration to the target area.

Chemical Instability and Stability

By chemical instability of one or more active agents is meant that at least one of the one or more active agents is susceptible to one or more of inter alia reaction, breakdown, ionization or oxidation or the rate thereof is increased when incorporated into a pharmaceutical or cosmetic carrier that is non aqueous or substantially non aqueous and not comprising a modulating agent.

Conversely by chemical stability of one or more active agents is meant that at least one of the one or more active agents is less susceptible to one or more of inter alia reaction, breakdown, ionization or oxidation or the rate thereof is impeded when incorporated into a pharmaceutical or cosmetic carrier that is non aqueous or substantially non aqueous and comprising a modulating agent.

Other foamable compositions are described in: U.S. Publication No. 05-0232869, published on Oct. 20, 2005, entitled NONSTEROIDAL IMMUNOMODULATING KIT AND COMPOSITION AND USES THEREOF; U.S. Publication No. 05-0205086, published on Sep. 22, 2005, entitled RETINOID IMMUNOMODULATING KIT AND COMPOSITION AND USES THEREOF; U.S. Publication No. 06-0018937, published on Jan. 26, 2006, entitled STEROID KIT AND FOAMABLE COMPOSITION AND USES THEREOF; U.S. Publication No. 05-0271596, published on Dec. 8, 2005, entitled VASOACTIVE KIT AND COMPOSITION AND USES THEREOF; U.S. Publication No. 06-0269485, published on Nov. 30, 2006, entitled ANTIBIOTIC KIT AND COMPOSITION AND USES THEREOF; U.S. Publication No. 07-0020304, published on Jan. 25, 2007, entitled NON-FLAMMABLE INSECTICIDE COMPOSITION AND USES THEREOF; U.S. Publication No. 06-0193789, published on Aug. 31, 2006, entitled FILM FORMING FOAMABLE COMPOSITION; U.S. patent application Ser. No. 11/732,547, filed on Apr. 4, 2007, entitled ANTI-INFECTION AUGMENTATION OF FOAMABLE COMPOSITIONS AND KIT AND USES THEREOF; U.S. Provisional Patent Application No. 60/789,186, filed on Apr. 4, 2006, KERATOLYTIC ANTIFUNGAL FOAM; U.S. Provisional Patent Application No. 0/815,948, filed on Jun. 23, 2006, entitled FOAMABLE COMPOSITIONS COMPRISING A CALCIUM CHANNEL BLOCKER, A CHOLINERGIC AGENT AND A NITRIC OXIDE DONOR; U.S. Provisional Patent Application No. 60/818,634, filed on Jul. 5, 2006, entitled DICARBOXYLIC ACID FOAMABLE VEHICLE AND PHARMACEUTICAL COMPOSITIONS THEREOF; U.S. Provisional Patent Application No. 60/843,140, filed on Sep. 8, 2006, entitled FOAMABLE VEHICLE AND VITAMIN PHARMACEUTICAL COMPOSITIONS THEREOF, all of which are incorporated herein by reference in their entirety. More particularly any of the active ingredients; the solvents; the surfactants; foam adjuvants; polymeric agents, penetration enhancers; preservatives, humectants; moisturizers; and other excipients as well as the propellants listed therein can be applied herein and are incorporated by reference.

The invention is described with reference to the following examples. This invention is not limited to these examples and experiments. Many variations will suggest themselves and are within the full intended scope of the appended claims.

Methodology

The formulas of the present invention may be made in the following general way with appropriate adjustments for each formulation as will be appreciated by someone skilled in the art. Polymers, if any, are mixed, swelled and solubilized in the waterless medium, when necessary, with appropriate heat until it forms a clear solution. Stabilizing surfactants added

usually with heat, until a homogeneous mixture is obtained, the mixture is then allowed to cool. The remainder of the ingredients, are then added with mixing until they have dissolved in the medium. The active agent is usually added at the end once the modulating agent has been incorporated. For foam the canisters are then filled with the above waterless formula, sealed and crimped with a valve and pressurized with the propellant.

A general procedure for preparing foamable compositions is set out in WO 2004/037225, which is incorporated herein by reference.

Waterless Foam

1. Dissolve the polymers, if any, in the main solvent with heating or cooling as appropriate for specific polymer. Add the all other ingredients and heat to 75° C. to melt and dissolve the various ingredients.
 2. Cool to below 40° C. and add sensitive ingredients with mild mixing.
 3. Cool to room temperature.
- Note that for substantially waterless foam a small amount of water is added before step 2.

Oily Waterless Foam

1. Mix all ingredients excluding polymers and heat to 75° C. to melt and dissolve and obtain homogeneous mixture.
 2. Mix well and cool to below 40° C. and add the polymers, if any, and sensitive ingredients with moderate mixing.
 3. Cool to room temperature.
- Note that for substantially waterless foam a small amount of water is added before step 2.

Oily Foam with Phospholipids

1. Swell the phospholipids in the main oily solvent under mixing for at least 20 minutes until uniform suspension is obtained.
 2. Add all other ingredients excluding polymers and heat to 75° C. to melt and dissolve and obtain homogeneous mixture.
 3. Mix well and cool to below 40° C. and add the polymers, if any, and sensitive ingredients with moderate mixing.
 4. Cool to room temperature.
 5. In case of polymers dissolved or organic solvent, dissolve the polymers in the solvent with heating or cooling as appropriate for specific polymer and add to the oily mixture under vigorous mixing at ~40° C.
- Note that for substantially waterless foam a small amount of water is added step 5.

Production Under Vacuum

Optionally, the foamable formulation may be produced under nitrogen and under vacuum. Whilst the whole process can be carried out under an oxygen free environment, it can be sufficient to apply a vacuum after heating and mixing all the ingredients to obtain an emulsion or homogenous liquid. Preferably the production chamber is equipped to apply a vacuum but if not the formulation can be for example placed in a dessicator to remove oxygen prior to filling and crimping.

Canisters Filling and Crimping

Each aerosol canister is filled with PFF and crimped with valve using vacuum crimping machine. The process of applying a vacuum will cause most of the oxygen present to be eliminated. Addition of hydrocarbon propellant may without being bound by any theory further help to reduce the likelihood of any remaining oxygen reacting with the active ingredient. It may do so, without being bound by any theory, by one or more of dissolving in the oil or hydrophobic phase of the formulation, by dissolving to a very limited extent in the aqueous phase, by competing with some oxygen from the formulation, by diluting out any oxygen, by a tendency of

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oxygen to occupy the dead space, and by oxygen occupying part of the space created by the vacuum being the unfilled volume of the canister or that remaining oxygen is rendered substantially ineffective in the formulation.

Pressurizing

Propellant Filling

Pressurizing is carried out using a hydrocarbon gas or gas mixture. Canisters are filled and then warmed for 30 sec in a warm bath at 50° C. and well shaken immediately thereafter.

Closure Integrity Test.

Each pressurized canister is subjected to bubble and crimping integrity testing by immersing the canister in a 60° C. water bath for 2 minutes. Canisters are observed for leakage as determined by the generation of bubbles. Canisters releasing bubbles are rejected.

Tests

By way of non limiting example the objectives of hardness, collapse time and FTC stability tests are briefly set out below as would be appreciated by a person of the art.

Hardness

LFRA100 instrument is used to characterize hardness. A probe is inserted into the test material. The resistance of the material to compression is measured by a calibrated load cell and reported in units of grams on the texture analyzer instrument display. Preferably at least three repeat tests are made. The textural characteristics of a dispensed foam can affect the degree of dermal penetration, efficacy, spreadability and acceptability to the user. The results can also be looked at as an indicator of softness. Note: the foam sample is dispensed into an aluminum sample holder and filled to the top of the holder.

Collapse Time

Collapse time (CT) is examined by dispensing a given quantity of foam and photographing sequentially its appearance with time during incubation at 36° C. It is useful for evaluating foam products, which maintain structural stability at skin temperature for at least 1 min.

Viscosity

Viscosity is measured with Brookfield LVDV-II+PRO with spindle SC4-25 at ambient temperature and 10, 5 and 1 RPM. Viscosity is usually measured at 10 RPM. However, at about the apparent upper limit for the spindle of →50,000 CP, the viscosity at 1 RPM may be measured, although the figures are of a higher magnitude.

Conductance

The conductance meter is calibrated. The electrode is inserted into a sufficient volume of composition and the conductance reading is recorded. Measurements with foamable compositions are made prior to addition of propellant. FTC (Freeze Thaw Cycles)

To check the foam appearance under extreme conditions of repeated cycles of cooling, heating, (first cycle) cooling, heating (second cycle) etc., commencing with -100° C. (24 hours) followed by +400° C. (24 hours) measuring the appearance and again repeating the cycle for up to three times. Focus Group

Five healthy volunteers selected at random were give a sample of foam formulation and applied it to the skin on their forearm and were asked to complete a questionnaire.

Chemical Stability

The amount of active agent present is analysed in foam expelled from various pressurized canisters containing foam formulations using HPLC. Analysis is carried out at zero time and at appropriate time intervals thereafter. The canisters are stored in controlled temperature incubators at 5 C, at 25 C, at,

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40 C and at 50 C. At appropriate time intervals canisters are removed and the amount of active agent in the foam sample is measured.

Analysis

About 1 g of foam or pre-foam formulation is dissolved in 0.1% acetic acid in methanol (diluent), to which internal standard (IS) solution is added. BMV, BMV-21 and IS are extracted by heating, cooling and centrifugation of the sample solution. The clear layer is analyzed by UPLC using a C-18 column; elution is performed with a mobile phase containing acetonitrile:water 55:45. The content of BMV and BMV-21 is calculated using the respective peak area ratio against average peak area ratio of BMV standard (0.2 mg/mL) to the IS present in the standard solution at the same concentration as in samples. The details of the method conditions are as follows: the column type is Acquity BEH C-18, 1.7 µm, 50×2.1 mm in 40° C., the flow is 0.5 mL/min, the detector: UV, at 254 nm injection volume is 4 µL; the diluents is 0.1% acetic acid in water: acetonitrile, 45:55 (v/v) and the mobile phase content is water: acetonitrile, 45:55 (v/v). The run time is 4 min. The method can be carried out by HPLC using a different but appropriate column of the same type.

Bubble Size

Foams are made of gas bubbles entrapped in liquid. The bubble size and distribution reflects in the visual texture and smoothness of the foam. Foam bubbles size is determined by dispensing a foam sample on a glass slide, taking a picture of the foam surface with a digital camera equipped with a macro lens. The diameter of about 30 bubbles is measured manually relatively to calibration standard template. Statistical parameters such as mean bubble diameter, standard deviation and quartiles are then determined. Measuring diameter may also be undertaken with image analysis software. The camera used was a Nikon D40X Camera (resolution 10MP) equipped with Sigma Macro Lens (ref: APO MACRO 150 mm F2.8 EX DG HSM). Pictures obtained are cropped to keep a squared region of 400 pixels×400 pixels.

Stock Compositions

Non-limiting examples of how stock solutions are made up with and without API are illustrated. Other stock solutions may be made using the same methodology by simply varying adding or omitting ingredients as would be appreciated by one of the ordinary skills in the art.

EXAMPLES

The invention is described with reference to the following examples. For the purpose of the Examples below it was sufficient to apply a vacuum only at the crimping stage although for long term stability preferably any vacuum should be applied during manufacture as well at a sufficient pressure so that any oxygen remaining in the formulation is virtually negligible. This invention is not limited to these examples and experiments. Many variations will suggest themselves and are within the full intended scope of the appended claims.

Example 1

A Waterless Steroid Foamable Composition with Out a Modulating Agent

The components of this waterless foamable composition and the results of the measurements of the stability of the active agent are set out below:

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Material chemical name	% W/W
Propylene glycol	31.60
Glycerin anhydrous	37.40
Stearyl alcohol	1.00
Hydroxypropyl cellulose	1.50
Laureth-4	2.00
Glyceryl Monostearate/PEG 100 Stearate	1.50
Stock solution	0.12
Betamethasone 17-Valerate	
Propylene glycol	24.88
Total	100.00

ACCELERATED CHEMICAL STABILITY TESTS FOR FOAM

Time point	% of BMV-17 (w/w)	% BMV-21 of BMV 0.12% (w/w)
ZT	0.120	0.32
2 weeks, 40° C.	0.079	33.98
1 month, 40° C.	0.066	40.07

ACCELERATED CHEMICAL STABILITY TESTS FOR PRE-FOAM FORMULATION

Time point	% of BMV-17 (w/w)	% BMV-21 of BMV 0.12% (w/w)
ZT	0.120	0.63
2 weeks, 50° C.	0.059	51.33
1 month, 50° C.	0.036	41.77

Comment: Significant amounts of BMV-17 break down into its unwanted isomer BMV-21 within a relatively short period of time in the absence of a Modulating agent. For foam, a propellant, which is a mixture of propane, butane and isobutane was added at 8% by weight of the total composition.

Example 2

Waterless Steroid Foamable Compositions where the Modulating Agent is a Citric Acid/Sodium Citrate Buffer

The components of these waterless foamable compositions and the results of measurements of the properties of the resultant foams and of the stability of the active agent are set out below:

a) At 0.1% Sodium Citrate

Material chemical name	% W/W
Propylene glycol	31.00
Glycerin anhydrous	37.40
Stearyl alcohol	1.00
Hydroxypropyl cellulose	1.50
Laureth-4	2.00
Glyceryl Monostearate/PEG 100 Stearate	1.50
Citric acid	0.50
Sodium citrate	0.10

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-continued

Material chemical name		% W/W
Stock solution	Betamethasone 17-Valerate	0.12
	Propylene glycol	24.88
Total Results		100.00
Quality		good
Color		white
Odor		No odor
Hardness [g]		66.98
Collapse time at 36° C. [sec]		>300

ACCELERATED CHEMICAL STABILITY TESTS FOR FOAM

Time point	% of BMV-17 (w/w)	% BMV-21 of BMV 0.12% (w/w)
ZT	0.117	0.90
2 weeks, 40° C.	0.118	0.42
1 month, 40° C.	0.111	0.47

ACCELERATED CHEMICAL STABILITY TESTS FOR PRE-FOAM FORMULATION

Time point	% of BMV-17 (w/w)	% BMV-21 of BMV 0.12% (w/w)
ZT	0.118	0.95
2 weeks, 50° C.	0.115	1.34
1 month, 50° C.	0.109	1.40

Comment: In the presence of a modulating agent BMV-17 does not significantly break down into its unwanted isomer BMV-21 over a period of a month of accelerated stability tests indicating that the formula will be stable in the long term. The presence of a classical buffer in the waterless composition of the present invention is effective in a non classical way in providing a chemically stable environment for the active agent. It will be noted that the formulation produced good quality breakable foam with typical physical parameters of a polar waterless foam. For foam, a propellant, which is a mixture of propane, butane and isobutane was added at 8% by weight of the total composition.

b) At 0.4% Sodium Citrate

Material chemical name	% W/W	
Propylene glycol	31.00	
Glycerin anhydrous	37.40	
Stearyl alcohol	1.00	
Hydroxypropyl cellulose	1.50	
Laureth-4	2.00	
Glyceryl Monostearate/PEG 100 Stearate	1.50	
Citric acid	0.50	
Sodium citrate	0.40	
Stock solution	Betamethasone 17-Valerate	0.12
	Propylene glycol	24.88
Total		100.00

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CHEMICAL STABILITY TESTS FOR FOAM		
Time point	% of BMV-17 (w/w)	% BMV-21 of BMV 0.12% (w/w)
ZT	0.122	0.00
2 weeks, 40° C.	0.117	0.82
1 month, 40° C.	0.117	1.89

CHEMICAL STABILITY TESTS FOR PRE-FOAM FORMULATION		
Time point	% of BMV-17 (w/w)	% BMV-21 of BMV 0.12% (w/w)
ZT	0.122	0.00
2 weeks, 50° C.	0.114	3.33
1 month, 50° C.	0.109	8.44

Comment: In the presence of a modulating agent BMV-17 does not significantly break down into its unwanted isomer BMV-21 over a period of two weeks of accelerated stability study. After a month minimal breakdown is seen indicating that the lower level of 0.1% w/w sodium citrate is preferable. For foam, a propellant, which is a mixture of propane, butane and isobutane was added at 8% by weight of the total composition.

Example 3

A Waterless Steroid Foamable Composition where the Modulating Agent is Stearic Acid

The components of this waterless foamable composition and the results of measurement of the stability of the active agent are set out below:

Material chemical name	% W/W
Propylene glycol	30.60
Glycerin anhydrous	37.40
Stearyl alcohol	1.00
Hydroxypropyl cellulose	1.50
Laureth-4	2.00
Glyceryl Monostearate/PEG 100 Stearate	1.50
Stearic acid	1.00
Stock solution Betamethasone 17-Valerate	0.12
Propylene glycol	24.88
Total	100.00

STABILITY TESTS FOR FOAM		
Time point	% of BMV-17 (w/w)	% BMV-21 of BMV 0.12% (w/w)
ZT	0.113	1.32
2 weeks, 40° C.	0.112	2.20
1 month, 40° C.	0.096	2.41

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STABILITY TESTS FOR PRE-FOAM FORMULATION		
Time point	% of BMV-17 (w/w)	% BMV-21 of BMV 0.12% (w/w)
ZT	0.115	0.73
2 weeks, 50° C.	0.109	4.80
1 month, 50° C.	0.093	5.78

Comment: In the presence of a modulating agent BMV-17 does not significantly break down into its unwanted isomer BMV-21 over a period of two weeks of accelerated stability. After a month only very minimal additional breakdown is seen indicating that stability is likely to be improved with a higher level of Stearic Acid and that the formula will be stable in the long term. For foam, a propellant, which is a mixture of propane, butane and isobutane was added at 8% by weight of the total composition.

Example-4

A Waterless Steroid Foamable Composition with a Penetration Enhancer DMI in the Absence of an Added Modulating Agent

The components of this waterless foamable composition and the results of measurements of the properties of the resultant foam and of the stability of the active agent are set out below:

a) Composition and Physical Results

Ingredient	% w/w
Stearyl alcohol	1.00
Laureth-4	2.00
Glyceryl stearate & PEG-100 stearate	1.50
Propylene glycol	45.88
Hydroxypropyl cellulose	1.50
Glycerin anhydrous	33.00
Dimethyl isosorbide	15.00
Betamethasone 17-valerate	0.12
Total:	100.00
Propellant: Mixture of propane, butane, isobutane*	8.00
Results	
Quality	good
Color	white
Odor	no odor
Density[g/mL]	0.089
Hardness [g]	94.610
Expansion time [sec]	90 sec
Collapse time at 36° C. [sec]	>300

b) Betamethasone Valerate Waterless Results Showing Stability at Three Months

	T-0	T-3	Temp
(w/w)%	0.117	0.113	25 C.
	0.117	0.113	40 C.
Percentage of original	100.000	96.581	25 C.
	100.000	96.581	40 C.

Comment: The above formula, in retrospect, was noted to have contained significant levels of residues of fatty acids,

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which were present in the raw materials. Nevertheless, the active ingredient did not significantly break down over a period of three months of accelerated stability indicating that the formula will be stable in the long term. Thus, the presence of acidic residues unexpectedly contributed to the stability of the active ingredient and it is postulated that the stabilizing effect in the above formula is a combination of the absence of water coupled with the presence of acidic residues in the formulation and weakly acidic properties of the surfactants. In contrast the formula of Example 1 utilizing pure grade raw materials with practically no acidic residues undergoes a relatively rapid and serious breakdown.

Example 5

A Waterless Vitamin D3 Derivative Foamable Composition where the Modulating Agent is Triethanolamine

The components of these waterless foamable compositions and the results of measurements of the properties of the resultant foams and of the stability of the active agent are set out below:

A. Where the waterless solvent is a combination of two polyethylene glycols:

Ingredient name (INCI, CTFA)	Concentration (% w/w)
Calcipotriol	0.005
Polyethylene glycol 400	65
Polyethylene glycol 200	32.925
Hydroxypropyl cellulose	0.5
Steareth-2	1.5
Triethanolamine	0.07

Results T-0

Quality	Good
Color	White
Odor	No odor
Density	0.096

B. Where the waterless solvent is a combination of two polyethylene glycols and propylene glycol:

Ingredient name (INCI, CTFA)	Concentration (% w/w)
Calcipotriol	0.005
Polyethylene glycol 400	65
Polyethylene glycol 200	27
Propylene glycol	4.895
Hydroxypropyl cellulose	1.5
Steareth-2	1.5
Triethanolamine	0.1

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Results T-0

Quality	Good
Color	White
Odor	No odor
Density	0.096

C. Where the waterless solvent is propylene glycol:

Ingredient name (INCI, CTFA)	Concentration (% w/w)
Calcipotriol	0.005
Propylene glycol	87.895
Stearyl alcohol	2
Hydroxypropyl cellulose	2
Laureth-4	2
Glyceryl monostearate	2
Ceteareth-20	1
PPG-15 Stearyl ether	3
Triethanolamine	0.1

Results T-0

Quality	Good
Color	White
Odor	No odor
Density	0.064

Comment: The above three formulations demonstrate waterless breakable foams of good quality in which the active ingredient is sensitive to the presence of water and light and is stabilized by the absence of water coupled with the presence of a modulating agent triethanolamine. As will be appreciated from the results the physical characteristics are little varied following variations in the waterless solvent. Moreover, it can be seen that waterless foamable pharmaceutical and cosmetic compositions of good quality can be achieved with minimal ingredients comprising a waterless solvent, a surfactant, a polymeric agent, a propellant and an effective amount of an active ingredient. For foam, a propellant, which is a mixture of propane, butane and isobutane was added at 8% by weight of the total composition. In the above examples the propellant was AP70.

Example 6

A Waterless Ascorbic Acid Foamable Composition

The components of these waterless foamable compositions and the results of measurements of the properties of the resultant foam and of the stability of the active agent are set out below:

	1	2	3	4
<u>Ingredient name (INCI, CTFA)</u>				
Propylene glycol	88.00	78.00	46.00	78.00
Glycerin anhydrous			33.00	10.00
Stearyl Alcohol	2.00	1.00	1.00	2.00
Hydroxypropyl Cellulose	2.00	1.50	1.50	2.00
Laureth-4	2.00	2.00	2.00	2.00
Glyceryl Monostearate/ PEG 100 Stearate			1.50	
GMS NE	2.00	1.00		2.00
Macrogol Cetostearyl ether	1.00	1.50		1.00
PPG-15 stearyl ether	3.00			3.00
Dimethyl isosorbide		15.00	15.00	
total	100.00	100.00	100.00	100.00
<u>Ingredient name (INCI, CTFA)</u>				
	% w/w	% w/w	% w/w	% w/w
Stock Gel Phase preparation	95.00	95.00	95.00	95.00
Ascorbic Acid	5.00	5.00	5.00	5.00
Propellant	8.00	8.00	8.00	8.00
RESULTS				
FOAM QUALITY	GOOD	GOOD	GOOD	GOOD
COLOR	WHITE	WHITE	WHITE	WHITE
ODOR	NO ODOR	ODOR	NO ODOR	ODOR
SHAKABILITY	MODERATE	MODERATE	MODERATE	MODERATE
DENSITY	0.08	0.09	0.10	0.08
COLLAPSE TIME	>300	>300	>300	>300
HARDNESS	Not measured	Not measured	52.25	36.04

Comments; the above formulations demonstrate the preparation of good quality foam containing ascorbic acid as active ingredient is not significantly influenced by the addition of a secondary solvent or the presence of a penetration enhancer Dimethyl isosorbide. To an extent ascorbic acid may act as its own modulating agent. Another modulating agent can be used to modify the artificial pH to be of the order of the pH at which ascorbic acid is most stable.

Example 7

Waterless Lidocaine HCl-Prilocaine Base Foamable Composition

The components of this waterless foamable composition and the results of measurements of the properties of the resultant foam and of the stability of the active agent are set out below:

Material chemical name	% W/W
Propylene glycol	46.00
Hydroxypropylcellulose EF	1.50
Stearyl alcohol	1.00
Laureth-4	2.00
Glyceryl Stearate (and) PEG-100 Stearate	1.50
Lidocaine HCl	2.50
Prilocaine base	2.50
Glycerin anhydrous	28.00
Dimethyl isosorbide	15.00
Total:	100.00
Mixture of Propane/Butane/Isobutane	8.00

RESULTS

FOAM QUALITY	GOOD
COLOR	WHITE
ODOR	NO ODOR
SHAKABILITY	GOOD
COLLAPSE TIME	>300
HARDNESS	85.88

Comments; the above formulations demonstrate the preparation of good quality foam containing anesthetics as active ingredient is not significantly influenced by the addition of a secondary solvent or the presence of a penetration enhancer Dimethyl isosorbide. To an extent lidocaine and prilocaine may act as its own modulating agent. Another modulating agent can be used to modify the artificial pH to be of the order of the pH at which lidocaine and prilocaine are respectively most stable.

Example 8

A Minimal Waterless Carrier

The components of this waterless foamable composition and the results of measurements of the properties of the resultant foam and of the stability of the active agent are set out below:

Material chemical name	% W/W
Propylene glycol	96.00
Hydroxypropyl cellulose	2.00
Steareth 2	2.00
Total	100.00

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-continued

Material chemical name	% W/W
Results	
quality	excellent
color	white
odor	no odor

Comment: this carrier produces an excellent foam. Addition of an active agent such as active steroids in low concentrations of the order of 0.01 to 0.5% for example BMV at 0.12% w/w, together with a modulating agent should have minimal effect on the physical characteristics of the resultant foam.

Example 9

Demonstration of Excellent Minimal Foams
Produced with Two Different Surfactants Steareth 2
and Montanov 68 (Cetearyl Alcohol and Cetearyl
Glucoside)

The components of these waterless foamable compositions and the results of measurements of the properties of the resultant foams and of the stability of the active agent are set out below:

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-continued

Material chemical name	% W/W	% W/W	% W/W
Cetearyl Glucoside and Cetearyl Alcohol			2.00
Betamethasone 17-Valerate	20.12		
Results			
Total quality	100.00	100.00	100.00
color	excellent	excellent	excellent
odor	white	white	white
shakability	no odor	no odor	no odor
	shakable	shakable	shakable

Comments: the above formulations demonstrate the preparation of excellent quality foams using two different non ionic surfactants and that the addition of buffer or active agent has no significant effect on foam quality. For foam, a propellant, which is a mixture of propane, butane and isobutane was added at 8% by weight of the total composition.

Example 10

Examples of Foams Containing a Steroid Active Agent with Carbomer (Synthetic High Molecular Weight Crosslinked Polymers of Acrylic Acid) as the Polymeric Agent

The components of these waterless foamable compositions and the results of measurements of the properties of the resultant foams and of the stability of the active agent are set out below:

Material chemical name	% W/W	% W/W	% W/W	% W/W	% W/W	% W/W	% W/W	% W/W
Propylene glycol	97.50	97.45	97.60	97.575	97.50	97.45	97.60	97.60
Steareth 2	2.00	2.00	2.00	2.00				
Carbomer 934	0.50	0.50	0.20	0.20	0.50	0.50	0.20	0.20
triethanolamine			0.20	0.20			0.20	0.20
Cetearyl Glucoside and Cetearyl Alcohol					2.00	2.00		
Methyl glucose sesquistearate							2.00	
Span 60								2.00
Clobetasol propionate		0.05				0.05		
Flucinolone acetonide				0.025				
Total	100.00	100.00	100.00	100.00	100.00	100.00		
Results								
Quality	.E	E	E	E	E	eE	.G	.G
E = excellent								
G = good								
Color	White	white	White	white	white	white	white	white
Odor	no odor	no odor	no odor	no odor	no odor	no odor	no odor	no odor
Shakability	yes.	yes	.yes	.yes	.yes	.yes	.yes	yes

Material chemical name	% W/W	% W/W	% W/W
Propylene glycol	96.00	95.28	97.50
Hydroxypropyl cellulose	2.00	2.00	0.50
Steareth 2	2.00	2.00	
Citric acid		0.50	
Sodium citrate		0.10	

Comments: the above formulations demonstrate the preparation of excellent quality foam using Carbomer (synthetic high molecular weight crosslinked polymers of acrylic acid). Carbomer is acidic in nature and can stabilize an active agent alone or in combination with an organic base such as triethanolamine. For foam, a propellant, which is a mixture of propane, butane and isobutane was added at 8% by weight of the total composition.

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Example 10

Chemical Stability

a) Stock Solutions 1 and 2

chemical name	Stock 1	Stock 2
Stearyl alcohol	1.00	
Laureth-4	2.00	
Glyceryl stearate & PEG-100 stearate	1.50	
Propylene glycol	36.00	9.88
Hydroxypropyl cellulose	1.50	
Glycerin anhydrous	33.00	
Steareth 2		
Dimethyl isosorbide	15.00	
Betamethasone 17-valerate		0.12
Total	90.00	10.00

Comments: 90 mls of Stock 1 was combined with 10 mls of stock 2 to produce the basic formulations of 3, 4 and 5 below to which only a few drops of acidic Modulating Agent was added as indicated below.

b) 46% Waterless PG Formulations with BMV with Different Acidic Modulating Agents Including One where the Modulating Agent is a Second Active Agent

	003	004	005
chemical name			
Stearyl alcohol	1.00	1.00	1.00
Laureth-4	2.00	2.00	2.00
Glyceryl stearate & PEG-100 stearate	1.50	1.50	1.50
Propylene glycol (PG)	45.88	45.88	45.88
Hydroxypropyl cellulose	1.50	1.50	1.50
Glycerin anhydrous	33.00	33.00	33.00
Dimethyl isosorbide	15.00	15.00	15.00
Betamethasone 17-valerate (BMV)	0.12	0.12	0.12
Lactic acid*	To ph 4-4.5		
L-Glutamic acid*		To ph 4-4.5	
Azelaic acid*			To ph 4-4.5
Total	100.00	100.00	100.00
Propellant (AP-70)	8.00	8.00	8.00
foam quality	Good	Good	Good
Color	White	White	White
Odor	No	No	No
assay (T-0) FOAM	0.1183	0.1183	0.1177
assay (T-1M) 5 C FOAM	0.1180	0.1182	0.1181
assay (T-1M) 25 C FOAM	0.1175	0.1185	0.1180
assay (T-1M) 40 C FOAM	0.1158	0.1156	0.1165
assay (T-1M) 50 C PFF	0.1148	0.1165	0.1158

*Only a few drops were required to achieve the required pH, which was sufficient to provide a stabilizing effect.

Comments: All the modulated formulations provided foam of good quality, in which the active agent BMV was shown to be stable to degradation in a wide range of temperature from

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5 C to 50 C over a period of a month. The pre foam formulation was also found to be stable for I month.

Example 11

EDTA

	006	007
chemical name		
Propylene glycol	97.90	98.90
Hydroxypropyl cellulose		1.00
Steareth 2	2.00	
EDTA	0.10	0.10
Total	100.00	100.00
Propellant (AP-70)	8.00	8.00
foam quality	Good	Good
Color	White	White
Odor	No	No

Comments: The formulation is modulated with EDTA and provided foam of good quality.

Example 12

Lysine

	008
chemical name	
Propylene glycol	98.00
Steareth 2	2.00
L-lysine	To ph 7
Total	100.00
Propellant (AP-70)	8.00
foam quality	Good
Color	White
Odor	No

Comments: The formulation modulated with a basic Modulating Agent provided foam of good quality,

Example 13

BMV

a) Minimum Ingredients;

	009	010
chemical name		
Stearyl alcohol	1.00	
Laureth-4	2.00	
Glyceryl stearate & PEG-100 stearate	1.50	
Propylene glycol	45.88	97.88
Hydroxypropyl cellulose	1.50	
Glycerin anhydrous	33.00	
Steareth 2	2.00	
Dimethyl isosorbide	15.00	
Betamethasone 17-valerate	0.12	0.12
Total	100.00	100.00
Propellant (AP-70)	8.00	8.00
Viscosity	4990.94	3711.21

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-continued

	009	010
foam quality	Good	Good
Color	White	White
Odor	No	No
Density	0.07	0.05
Collapse time	>300/G	.300/G
BUBBLE SIZE (μm)	150	139
BUBBLE SIZE (above 500 μm)	3.4	3.7
Conductivity	0.41 μS	0 μS
Conductivity (+1 drop of Lactic acid)	0.55 μS	0.05 μS

Comments: It is surprisingly possible to produce good quality foam without a polymeric agent. Nevertheless, the presence of polymeric agent can be not only helpful but important and sometimes critical for foam stability. Prophetically, small amounts of modulating agent may be added to the formulations without significant effect on the resultant foam. Remarkably, despite that these formulations are waterless, nevertheless a single drop of lactic acid results in a significant increase of conductivity. Also as can be seen herein the use of modulating agents is just as applicable for formulations with minimal ingredients as it is with complex formulations, perhaps the main difference being that with complex formulations there are more ingredients which increases the risk that one may contain a small impurity that can result in destabilization of the active ingredient. On the other hand formulations with few ingredients may have higher levels of a destabilizing impurity merely because say 90% of the formulation comprises an ingredient having the impurity albeit at low levels. Either way the importance of the presence of a small amount of modulating agent in a waterless formulation cannot be ignored or underestimated.

b) Focus Group (5)

		Sum	Avg	STDV	TOTAL
MAPG009P	ease of application	21	4.2	0.45	180
	foam Texture	20	4	0.00	
	foam stability on hand	24	4.8	0.45	
	absorbance (1 min.)	17	3.4	0.55	
	spreadability	21	4.2	0.45	
	greasy feeling (after 1-2 min.)	16	3.2	1.10	
	shiny look (after 1-2 min.)	18	3.6	1.14	
	stickiness (after 1-2 min.)	17	3.4	1.14	
	odor	10	2	1.73	
	total satisfaction	16	3.2	1.10	
MAPG010P	ease of application	21	4.2	0.84	201
	foam Texture	20	4	0.71	
	foam stability on hand	22	4.4	0.55	
	absorbance (1 min.)	19	3.8	1.10	
	spreadability	21	4.2	0.84	
	greasy feeling (after 1-2 min.)	19	3.8	1.30	
	shiny look (after 1-2 min.)	18	3.6	1.14	
	stickiness (after 1-2 min.)	18	3.6	1.14	
	odor	22	4.4	0.55	
	total satisfaction	21	4.2	0.84	

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Comments: The total satisfaction was surprisingly found to be significantly greater with the formulation with minimal ingredients.

Example 14

Carbopol and TEA

	011	012
chemical name		
Propylene glycol	99.00	97.00
Carbopol 934	1.00	1.00
Stearth 2		2.00
Triethanolamine (TEA)	neutralization (1 drop)	neutralization (1 drop)
Total	100.00	100.00
Propellant (AP-70)	8.00	8.00
Viscosity		13485.12
foam quality	P	Good
Color	White	White
Odor	No	No
Density		0.08
Collapse time		>300/G
BUBBLE SIZE (μm)		72
BUBBLE SIZE (above 500 μm)		0.0

Comments: The formulation modulated with an acidic polymer and a basic Modulating Agent TEA provided foam of good quality, Carbomer is a cross-linked polymer of acrylic acid with a high molecular weight.

Example 15

Stearic Acid

	013	014
chemical name		
Stearic acid	5.00	3.00
Isostearic acid		3.00
Propylene glycol	95.00	94.00
Total	100.00	100.00
Propellant (AP-70)	8.00	8.00
Viscosity	1887.60	
foam quality	Good	P
Color	White	White
Odor	No	No
Density	0.30	
Collapse time	>300/G	

Comments: Stearic acid a waxy solid acts as a foam adjuvant, thickener and Modulating Agent to produce good quality foam. The selection of Modulating Agent is not per se obvious with a waterless formulation. For example, the addition of isostearic acid results in poor foam presumably but without being bound by any theory suggested due to it being a liquid wax and not having the thickening effect of its closely related counterpart stearic acid plus its isostearic acids asymmetrical shape even though they both are C18.

What is claimed is:

1. A waterless composition comprising one or more active agents and a carrier, said carrier comprising
 - a) a modulating agent;
 - b) a polyol;
 - c) a surface active agent; and
 - d) a foam adjuvant;

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wherein the one or more active agents are chemically unstable in the carrier in the absence of a modulating agent;

wherein the modulating agent is capable of and is selected to modulate or adjust the artificial pH of the carrier to an artificial pH or to provide an artificial pH buffering effect such that the chemical stability of the at least one active agent is increased as compared to its stability in the carrier without the modulating agent

wherein if the waterless composition is packaged in a pressurized container and propellant is added the composition will be capable upon release of expanding to form a breakable foam.

2. The waterless composition of claim 1 further comprising one or more agents that additionally are capable of a function selected from the group consisting of chelating an available metal ion, impeding ionization, and impeding oxidation.

3. The waterless composition of claim 1 wherein the polyol comprises about 25% to about 98% by weight of the carrier.

4. The waterless composition of claim 3 further comprising a about 0.01% to about 5% by weight of at least one polymeric agent.

5. The waterless composition of claim 1, wherein the modulating agent is about 5% to about 0.01% by weight of the carrier.

6. The waterless composition of claim 1 further comprising a polar solvent, and a liquefied or compressed gas propellant at a concentration of about 3% to about 25% by weight of the composition.

7. The waterless composition of claim 1, wherein the modulating agent is selected from the group consisting of sodium citrate, citric acid, lactic acid, glutamic acid, ascorbic acid, azelaic acid, stearic acid, triethanolamine, lysine, lidocaine, prilocaine, carbomer and mixtures of any two or more thereof.

8. The waterless composition of claim 1, wherein the polyol is selected from the group consisting of a diol; a triol; at least one diol and at least one triol, wherein the ratio between the diol and triol is between 9:1 and 1:1; a saccharide; and mixtures thereof.

9. The waterless composition of claim 8, wherein the diol is selected from the group consisting of propylene glycol, butanediol, butenediol, butynediol, pentanediol, hexanediol, octanediol, neopentyl glycol, 2-methyl-1,3-propanediol, diethylene glycol, triethylene glycol, tetraethylene glycol, dipropylene glycol and dibutylene glycol; and or

wherein the triol is selected from the group consisting of glycerin, butane-1,2,3-triol, butane-1,2,4-triol and hexane-1,2,6-triol.

10. The waterless composition of claim 6, wherein the polar solvent is selected from the group consisting of dimethyl isosorbide, tetrahydrofurfuryl alcohol polyethyleneglycol ether, DMSO, a pyrrolidone, N-Methyl-2-pyrrolidone, 1-Methyl-2-pyrrolidinone, ethyl proxitol, dimethylacetamide, a PEG-type surfactant, an alpha hydroxy acid, lactic acid, and glycolic acid.

11. The waterless composition of claim 6, wherein the composition is substantially alcohol-free.

12. The waterless composition of claim 1, wherein the modulating agent is selected from the group consisting of an alpha hydroxyl acid, an aliphatic beta hydroxyacid, an aromatic acid, an aromatic hydroxyl acid, an alpha ketoacid, an aliphatic carboxylic acid, a branched aliphatic carboxylic acid, a short chain carboxylic acid, a fatty acid, an omega-3 fatty acid, an omega-6 fatty acid, an omega-9 fatty acid, a dicarboxylic acid, a branched dicarboxylic acid, an unsaturated dicarboxylic acid, an amino acid, a dimer or oligomer of

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amino acids, a retinoid, a nitrogen-containing organic compound, a primary, secondary, tertiary and quaternary amine, an amide, an amine oxide and a lactam.

13. The waterless composition of claim 12,

wherein the alpha hydroxyl acid and beta hydroxyl acid are selected from the group consisting of alpha-hydroxybutyric acid, alpha-hydroxyisobutyric acid, alpha-hydroxyisocaproic acid, alpha-hydroxyisovaleric acid, atrolactic acid, beta-hydroxybutyric acid, beta-phenyl lactic acid, beta-phenylpyruvic acid, citric acid, pyruvic acid, galacturonic acid, glucoheptonic acid, glucoheptono 1,4-lactone, gluconic acid, gluconolactone, glucuronic acid, glucuronolactone, glycolic acid, lactic acid, mandelic acid, mucic acid, pyruvic acid, saccharic acid, saccharic acid 1,4-lactone, tartaric acid and tartronic acid, 3-Hydroxybutanoic acid, quinic acid, isocitric acid, tropic acid, trethocanic acid, chlorolactic acid, citramalic acid, agaricic acid, aleuritic acid, pantoic acid, lactobionic acid, piscidic acid, hexulosonic acid or the anhydride thereof;

wherein the aromatic acid is selected from the group consisting of benzoic acid, toluic acid, dimethyl benzoic acid and phthalic acid;

wherein the beta hydroxyl acid is selected from the group consisting of salicylic acids and derivatives thereof;

wherein the alpha ketoacid has the molecular structure of



wherein Ra and Rb are independently selected from the group consisting of H and saturated or unsaturated, isomeric or non-isomeric, straight, branched, or cyclic C1-C25 alkyl, aralkyl, or aryl groups, wherein Ra may be optionally substituted with an F, Cl, Br, I, OH, CHO, COOH, or alkoxy group having 1 to 9 carbon atoms;

wherein the aliphatic carboxylic acid is selected from the group consisting of formic acid, acetic acid and propionic acid, butyric acid, butyric acid, caproic acid, caprylic acid, nonanoic acid, capric acid, lauric acid, myristic acid, palmitic acid, stearic acid, arachidic acid, behenic acid, octacosanoic acid, oleic acid, linoleic acid, alpha-linolenic acid, arachidonic acid, eicosapentaenoic acid, docosahexaenoic acid, erucic acid, valproic acid and 12-hydroxy stearic acid;

wherein the dicarboxylic acid is selected from the group consisting of oxalic acid, malonic acid, succinic acid, glutaric acid, adipic acid, pimelic acid, suberic acid, azelaic acid, sebacic acid, dodecanedioic acid, brassylic acid, thapsic acid, 14-methylnonacosanedioic acid, 14,15-dimethyltriacontanedioic acid (C30) undecylenic acid, maleic acid and fumaric acid;

wherein the carbon atom skeleton of the branched dicarboxylic acid is substituted with at least one group selected from the group consisting of R, F, Cl, Br, OH, OR, SH, CHO, COOH, and NRaRb, and wherein R, Ra and Rb are independently selected from the group consisting of H, saturated or unsaturated, isomeric or non-isomeric, straight, branched, or cyclic C1-C25 alkyl, aralkyl, or aryl groups;

wherein the branched dicarboxylic acid is selected from the group consisting of aspartic acid, alpha-ketoglutaric acid, adipic acid 2-amino, aconitic acid, benzene dicarboxylic acid, citramalic acid, citric acid, cystathionine, glucuronic acid, glutamic acid, itaconic acid, malic acid, mucic acid, oxalacetic acid, diamino pimelic acid, saccharic acid, dimethyl succinic acid, tartaric acid and tartronic acid;

wherein the carboxylic acid is selected from the group consisting of is selected from the group consisting of retinoic acid, isotretinoin, ascorbic acid, isoascorbic acid, ethanesulfonic acid, glycerophosphoric acid, acetohydroxamic acid, aconitic acid, alpha-ketocaproic acid, aminomalonic acid, hippuric acid, hydrochloric acid, methanesulfonic acid, oxalic acid, phosphoric acid, sorbic acid, iminodiacetic acid and carnitine; and

wherein the amino acid is selected from the group consisting of glycine, alanine, valine, leucine, isoleucine, serine, threonine, cysteine, methionine, aspartic acid, asparagine, glutamic acid, glutamine, arginine, lysine, histidine, phenylalanine, tyrosine, tryptophan, praline, B-alanine(3-alanine), 4-aminobutyrate (GABA), 3-cyanoalanine (B-cyanoalanine), 2-aminobutyric acid, 2-methylene-4-aminobutyric acid, 3-methylene-4-aminobutyric acid, 2-aminoisobutyric acid, 5-aminolevulinic acid, 2-amino-4-methylhexanoic acid (homoisoleucine), 2-amino-4-methylhex-4-enoic acid, 2-amino-4-methylhex-5-ynoic acid, 2-amino-3-methylpentanoic acid, 2-aminoadipic acid, 4-ethylideneglutamic acid, 3-aminoglutaric acid, 2-aminopimelic acid, N4-ethylasparagine, N4-methylasparagine, erythro-4-methylglutamic acid, 4-methyleneglutamic acid, 4-methylene-glutamine, N5-methylglutamine, N5-ethylglutamine (theanine), N5-isopropylglutamine, 2-amino-4-(aminoxy)butyric acid (canaline), 2,4-diaminobutyrate, N4-acetyl-2,4-diaminobutyrate, N4-lactyl-2,4-diaminobutyrate, N4-oxalyl-2,4-diaminobutyrate, 2,3-diaminopropionic acid, N3-acetyl-2,3-diaminopropionic acid, N3-methyl-2,3-diaminopropionic acid, N3-oxalyl-2,3-diaminopropionic acid, N6-acetyllysine, N6-methyllysine, N6-trimethyllysine (laminine), ornithine (2,5-diaminopentanoic acid), saccharopine (N6-(2'-glutamyl)lysine, 2,6-diaminopimelic acid, N4-(2-hydroxyethyl)asparagine, erythro-3-hydroxyaspartic acid, 4-hydroxyarginine, 4-hydroxycitrulline, threo-4-hydroxyglutamic acid, 3,4-dihydroxyglutamic acid, 3-hydroxy-4-methylglutamic acid, 3-hydroxy-4-methyleneglutamic acid, 4-hydroxy-4-methylglutamic acid, 4-hydroxy-glutamine, N5-(2-hydroxyethyl)glutamine, 5-hydroxynorleucine, threo-4-hydroxyhomoarginine, homoserine, O-acetylhomoserine, O-oxalylhomoserine, O-phosphohomoserine, 4-hydroxyisoleucine, 5-hydroxymethylhomocysteine, threo-3-hydroxy-leucine, 5-hydroxy-leucine, 2-hydroxylysine, 4-hydroxylysine, 5-hydroxylysine, N6-acetyl-5-hydroxylysine, N6-trimethyl-5-hydroxylysine, 4-hydroxyornithine, mimosine, 4-hydroxynorvaline, 5-hydroxynorvaline, 2-amino-4,5-dihydroxypentanoic acid, 2-amino-4-hydroxypimelic acid, 4-hydroxyvaline, O-acetylserine, O-phosphoserine, pipecolic acid, (piperidine-2-carboxylic acid), 3-hydroxypipecolic acid, trans-4-hydroxypipecolic acid, trans-5-hydroxypipecolic acid, 5-hydroxy-6-methylpipecolic acid, 4,5-dihydroxypipecolic acid, trans-3-hydroxyproline, trans-4-hydroxyproline, trans-4-hydroxymethylproline, azetidine-2-carboxylic acid, N-(3-amino-3-carboxypropyl)azetidine-2-carboxylic acid, 4,5-dehydropipecolic acid (baikaiin), 3-amino-3-carboxypyrrolidone (cucurbitine), 2-(cyclopent-2'-enyl)glycine, 5-hydroxytryptophan, albizziine (2-amino-3-ureidopropionic acid), arginosuccinic acid, canavinosuccinic acid, citrulline, homoarginine, homocitrulline, indospicine, O-ureidohomoserine, 6-hydroxykynurenine, 3-(4-aminophenyl)alanine, 3-(3-aminomethylphenyl)alanine, 3-(3-carboxyphenyl)alanine, 3-carboxytyrosine, 3-(3-

hydroxymethylphenyl)alanine, 3-(3-hydroxyphenyl)alanine, 3-(3,4-dihydroxyphenyl)alanine (L-DOPA), 2-(phenyl)glycine, 2-(3-carboxyphenyl)glycine, 2-(3-carboxy-4-hydroxyphenyl)glycine, 2-(3-hydroxyphenyl)glycine, 2-(3,5-dihydroxyphenyl)glycine, 4-aminopipecolic acid, guvacine, 2-amino-4-(isoxazolin-5-one)-2-yl)butyric acid, lathyrine, tetrahydrolathyrine and ornithin and dimers or oligomers thereof.

14. The waterless composition of claim 12, wherein the modulating agent is a nitrogen-containing organic compound selected from the group consisting of primary amines, methylamine and ethylamine; an ethanolamine, monoethanolamine, monoisopropanolamines, a diamine, ethylenediamine, 1,2-diaminopropane, a dialkylamine, dimethylamine, diethylamine, diethanolamine, diisopropanolamine, N-methylethanolamine, N-ethylethanolamine, a tertiary amine, a trialkylamine, triethylamine, triethylamine, triethanolamine, N-methyldiethanolamine and tri-isopropanolamine.

15. The waterless composition of claim 4, wherein the polymeric agent is selected from the group consisting of a locust bean gum, a sodium alginate, a sodium caseinate, an egg albumin, a gelatin agar, a carrageenin gum, a xanthan gum, a quince seed extract, a tragacanth gum, a guar gum, a cationic guar, a hydroxypropyl guar gum, a starch, an amine-bearing polymer, a chitosan, an alginic acid, a hyaluronic acid, a chemically modified starch, a carboxyvinyl polymer, a polyvinyl alcohol, a polyacrylic acid polymer, a polymethacrylic acid polymer, a polyvinyl acetate, a polyvinyl chloride polymer, a polyvinylidene chloride polymer, a methylcellulose, a hydroxypropyl cellulose, a hydroxypropyl methylcellulose, a hydroxyethyl cellulose, a methylhydroxyethylcellulose, a hydroxyethylcarboxymethylcellulose, a carboxymethyl cellulose, a cationic cellulose, a PEG 1000, a PEG 4000, a PEG 6000, a PEG 8000, and a carbomer.

16. The waterless composition of claim 6, wherein the polymeric agent is dispersible in the polyol or in the mixture of a polyol and the polar solvent.

17. The waterless composition of claim 1, wherein the surface active agent comprises at least one surfactant selected from the group consisting of a polyoxyethylene fatty ether, a polyoxyethylene fatty ester, a carbohydrate ester and a sucrose ester, glyceryl stearate, PEG-100 stearate, steareth-2, steareth-20, steareth-21, cetareth 2, PEG-100 stearyl ether, cetaryl glucoside, methyl glucose sesquisteate, sorbitan monostearate, GMS NE, span 20, glyceryl stearate and PEG 100 stearate, glyceryl stearate and PEG 100 stearate and laureth4; steareth 2, PEG 100 searate and laureth4, and cetaryl glucoside and cetaryl alcohol.

18. The waterless composition of claim 1, wherein the surface active agent comprises a non-ionic surface active agent or a mixture of at least one non-ionic surfactant and at least one ionic surfactant in a ratio selected from a) 100:1 to about 6:1 and b) about 1:1 to about 6:1.

19. The waterless composition of claim 3, further comprising a hydrophobic solvent.

20. The waterless composition of claim 19, wherein the hydrophobic solvent is selected from the group consisting of mineral oil, isopropyl palmitate, isopropyl isostearate, diisopropyl adipate, diisopropyl dimerate, maleated soybean oil, octyl palmitate, cetyl lactate, cetyl ricinoleate, tocopheryl acetate, acetylated lanolin alcohol, cetyl acetate, phenyl trimethicone, glyceryl oleate, tocopheryl linoleate, wheat germ glycerides, arachidyl propionate, myristyl lactate, decyl oleate, ricinoleate, isopropyl lanolate, pentaerythrityl tetrastearate, neopentylglycol dicaprylate/dicaprate, isononyl isononanoate, isotridecyl isononanoate, myristyl myristate, triisocetyl citrate, octyl dodecanol, unsaturated or polyun-

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saturated oils, such as olive oil, corn oil, soybean oil, canola oil, cottonseed oil, coconut oil, sesame oil, sunflower oil, borage seed oil, syzigium aromaticum oil, hempseed oil, herring oil, cod-liver oil, salmon oil, flaxseed oil, wheat germ oil, evening primrose oils; essential oils; and silicone oils, dimethicone, cyclomethicone, polyalkyl siloxane, polyaryl siloxane, polyalkylaryl siloxane, a polyether siloxane copolymer and a poly(dimethylsiloxane)-(diphenyl-siloxane) copolymer.

21. The waterless composition of claim 1, wherein the foam adjuvant is selected from the group consisting of a fatty alcohol, a fatty acid and a hydroxyl fatty acid.

22. The waterless composition of claim 1, further comprising an additional component selected from the group consisting of an anti perspirant, an anti-static agent, a buffering agent, a bulking agent, a chelating agent, a colorant, a conditioner, a deodorant, a diluent, a dye, an emollient, fragrance, a humectant, an occlusive agent, a penetration enhancer, a perfuming agent, a permeation enhancer, a preservative, a skin penetration enhancer, a sunscreen, a sun blocking agent, a sunless tanning agent, and a vitamins.

23. The waterless composition of claim 1, wherein the active agent is selected from the group consisting of active herbal extracts, acaricides, age spot and keratose removing agents, allergen, analgesics, local anesthetics, antiacne agents, antiallergic agents, antiaging agents, antiinfective, antibacterials, antibiotics, antburn agents, anticancer agents, antidandruff agents, antidepressants, antidermatitis agents, antiedemics, antifungal, antihistamines, antihelminths, anti-hyperkeratolyte agents, antiinflammatory agents, antiirritants, antilipemics, antimicrobials, antimycotics, antiproliferative agents, antiparasitic agents, antioxidants, anti-wrinkle agents, antipruritics, antipsoriatic agents, antirosacea agents, antiseborrheic agents, antiseptic, antismelling agents, antiviral agents, anti-yeast agents, agents that control yeast, astringents, topical cardiovascular agents, chemotherapeutic agents, corticosteroids, dicarboxylic acids, disinfectants, fungicides, hair growth regulators, hormones, hydroxy acids, immunosuppressants, immunoregulating agents, insecticides, insect repellents, keratolytic agents, lactams, metals, metal oxides, mitocides, neuropeptides, non-steroidal anti-inflammatory agents, oxidizing agents, pediculicides, photodynamic therapy agents, retinoids, sanatives, scabicides, self tanning agents, steroids, skin whitening agents, asoconstrictors, vasodilators, vitamins, vitamin D derivatives, flavonoids, wound healing agents and wart removers.

24. The waterless composition of claim 23, wherein the steroid is selected from the group consisting of alclometasone dipropionate, amcinafel, amcinafide, amcinonide, beclomethasone, beclomethasone dipropionate, betamethasone, betamethasone benzoate, betamethasone dexamethasone-phosphate, dipropionate, betamethasone valerate, budesonide, chloroprednisone, chlorprednisone acetate, clescinolone, clobetasol, clobetasol propionate, clobetasol valerate, clobetasone, clobetasone butyrate, clocortelone, cortisone, cortodoxone, craposone butyrate, desonide, desoxymethasone, dexamethasone, desoxycorticosterone acetate, dichlorisone, diflorasone diacetate, diflucortolone valerate, diflurosone diacetate, diflurprednate, fluadrenolone, flucetonide, flucoronide, flucorolone acetonide, flucortine butylesters, fludroxycortide, fludrocortisone, flumethasone, flumethasone pivalate, flumethasone pivalate, flunisolide, fluocinolone, fluocinolone acetonide, fluocinonide, fluocortin butyl, fluocortolone, fluorometholone, fluosinolone acetonide, fluperolone, fluprednidene acetate, fluprednisolone hydrocortamate, fluradrenolone, fluradrenolone acetonide, flurandrenolone, fluticasone, halcinonide, halobetasol,

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hydrocortisone, hydrocortisone acetate, hydrocortisone butyrate, hydrocortisone cyclopentylpropionate, hydrocortisone valerate, hydroxyltriamcinolone, medrysone, meprednisone, .alpha.-methyl dexamethasone, methylprednisolone, methylprednisolone acetate, mometasone furoate, paramethasone, prednisolone, prednisone, pregnenolone, progesterone, spironolactone, triamcinolone, triamcinolone acetonide and derivatives, esters and salts thereof;

wherein the antifungal agent is selected from the group consisting of a polyene, natamycin, nystatin; an allylamine, naftifine, terbinafine; an imidazole, bifonazole, clotrimazole, econazole, fenticonazole, ketocanazole, miconazole, oxiconazole; a diazole, a triazoles, fluconazole, itraconazole, terconazole, tolnaftate, ciclopirox, undecylenic acid, sulbentine, griseofulvin, Amphotericin B, flucytosine (5FC), a morpholine compound, amorolfine, and the related morpholines and analogs, derivatives and salts thereof, and any combination thereof at a therapeutically effective concentration; and

wherein the antibacterial agent is selected from the group consisting of a beta-lactam antibiotic, an aminoglycoside, an ansa-type antibiotic, an anthraquinone, an azole, metronidazole, an antibiotic glycopeptide, a macrolide, erythromycin, clindamycin, an antibiotic nucleoside, an antibiotic peptide, polymyxin B, an antibiotic polyene, an antibiotic polyether, an antibiotic quinolone, an antibiotic steroid, fucidic acid, mupirocin, chloramphenicol, a sulfonamide, tetracycline, an antibiotic metal, silver, copper, zinc, mercury, tin, lead, bismuth, cadmium, chromium, an oxidizing agent, iodine, iodate, a periodate, a hypochlorite, a permanganate, a substance that release free radicals and/or active oxygen, a cationic antimicrobial agent, a quaternary ammonium compound, a biguanide, chlorohexidine, a triguanide, a bisbiguanide, a polymeric biguanide, a naturally occurring antibiotic compound and analogs, derivatives, salts, ions and complexes thereof.

25. The waterless composition of claim 1, wherein the active agent is unstable in the presence of water.

26. The waterless composition of claim 1, wherein the active agent is stable at an acidic pH range and the modulating agent is acidic.

27. The waterless composition of claim 1, wherein the active agent is an ester, which undergoes hydrolysis at basic pH.

28. The waterless composition of claim 1, wherein the active agent is a compound, which undergoes rearrangement at basic pH.

29. The waterless composition of claim 1, wherein the active agent is stable at a basic pH range and the modulating agent is basic.

30. The waterless composition of claim 29, wherein the active agent is selected from vitamin D, a vitamin D analog, a vitamin D derivative.

31. The waterless composition of claim 1, wherein the modulating agent is a nitrogen-containing modulating agent.

32. The waterless composition of claim 1, wherein the modulating agent is triethanolamine and the active agent is calcipotriol.

33. The waterless composition of claim 1, wherein the modulating agent is selected from the group consisting of sodium citrate, citric acid, lactic acid, glutamic acid, azaleic acid, ascorbic acid, stearic acid and mixtures of any two or more thereof and the active agent is Betamethasone 17-valerate (bmV).

34. The waterless composition of claim 1, wherein the modulating agent is selected from the group consisting of

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carbomer, and triethanolamine, and mixtures thereof and the active agent is selected from the group consisting of clobetolol propionate and flucinolone acetonide.

35. The waterless composition of claim 1, wherein the active agent is stable at about neutral pH range and the modulating agent is neutral.

36. The waterless composition of claim 1, wherein the modulating agent is a pharmaceutical or cosmetic active agent.

37. A method of treating a disorder of mammalian subject, comprising:

administering a composition to a target site, the composition comprising the composition of claim 1, wherein the target site is selected from the group consisting of the skin, a body cavity, a mucosal surface, the nose, the mouth, the eye, the ear canal, the respiratory system, the vagina and the rectum.

38. The method of claim 37, wherein the composition further comprises a polymeric agent and or a polar solvent.

39. The method of claim 38, wherein the disorder is selected from the group consisting of dermatological pain, dermatological inflammation, acne, acne *vulgaris*, inflammatory acne, non-inflammatory acne, acne fulminans, nodular papulopustular acne, acne conglobata, dermatitis, bacterial skin infections, fungal skin infections, viral skin infections, parasitic skin infections, skin neoplasia, skin neoplasms, pruritis, cellulitis, acute lymphangitis, lymphadenitis, erysipelas, cutaneous abscesses, necrotizing subcutaneous infections, scalded skin syndrome, folliculitis, furuncles, hidradenitis suppurativa, carbuncles, paronychia infections, rashes, erythrasma, impetigo, ecthyma, yeast skin infections, warts, molluscum contagiosum, trauma or injury to the skin, post-operative or post-surgical skin conditions, scabies, pediculosis, creeping eruption, eczemas, psoriasis, *pityriasis rosea*, lichen planus, *pityriasis rubra pilaris*, edematous, erythema multiforme, erythema nodosum, granuloma annulare, epidermal necrolysis, sunburn, photosensitivity, *pemphigus*, bullous pemphigoid, dermatitis herpetiformis, keratosis pilaris, calluses, corns, ichthyosis, skin ulcers, ischemic necrosis, miliaria, hyperhidrosis, moles, Kaposi's sarcoma, melanoma, malignant melanoma, basal cell carcinoma, squamous cell carcinoma, poison ivy, poison oak, contact dermatitis, atopic dermatitis, rosacea, purpura, moniliasis, candidiasis, baldness, alopecia, Behçet's syndrome, cholesteatoma, Dercum disease, ectodermal dysplasia, gustatory sweating, nail patella syndrome, lupus, hives, hair loss, Hailey-Hailey disease, chemical or thermal skin burns, *scleroderma*, aging skin, wrinkles, sun spots, necrotizing fasciitis, necrotizing myositis, gangrene, scarring, and vitiligo, *chlamydia* infection, gonorrhea infection, hepatitis B, herpes, HIV/AIDS, human papillomavirus (HPV), genital warts, bacterial vaginosis, candidiasis, chancroid, granuloma Inguinale, lymphogranuloma venereum, mucopurulent cervicitis (MPC), molluscum contagiosum, nongonococcal urethritis (NGU), trichomoniasis, vulvar disorders, vulvodynia, vulvar pain, yeast infection, vulvar dystrophy, vulvar intraepithelial neoplasia (VIN), contact dermatitis, pelvic inflammation, endometritis, salpingitis, oophoritis, genital cancer, cancer of the cervix, cancer of the vulva, cancer of the vagina, vaginal dryness, dyspareunia, anal and rectal disease, anal abscess/fistula, anal cancer, anal fissure, anal warts, Crohn's disease, hemorrhoids, anal itch, pruritus ani, fecal incontinence, constipation, polyps of the colon and rectum; and wherein the active agent is suitable for treating said disorder.

40. The composition of claim 3, comprising about 0.05% to about 10% by weight of the carrier of the surface active agent.

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41. A waterless composition comprising:

at least one active agent and a carrier comprising

a) a modulating agent;

b) a polyol;

c) a surface active agent;

d) a foam adjuvant; and

e) a liquefied or compressed gas propellant at a concentration of about 3% to about 25% by weight of the composition

wherein the at least one active agent is chemically unstable in the carrier in the absence of a modulating agent;

wherein the modulating agent comprises an effective amount of one or more agents that are capable of impeding said destabilization and or are capable of stabilizing the active agent by chelating a metal ion such that the modulating agent is capable of reducing in the waterless carrier the availability of metal ions so the stability of at least one active agent is improved when compared to its stability in the carrier without the modulating agent; and wherein the composition is stored in a pressurized container and upon release expands to form a breakable foam.

42. The waterless composition of claim 41 further comprising one or more agents that additionally are capable of impeding said destabilization and or are capable of stabilizing the active agent primarily by modulating or adjusting the artificial pH of the carrier such that the modulating agent is capable of producing in the waterless carrier an artificial pH or an artificial pH buffering effect at about a pH or pH range in which the stability of at least one active agent is improved when compared to its stability in the carrier without the modulating agent and or by impeding ionization and or by impeding oxidation.

43. The waterless composition of claim 41, wherein the modulating agent is a chelating agent.

44. The waterless composition of claim 41, wherein the chelating agent is sufficiently soluble or functional in the waterless solvent to enable it to "mop up" or "lock" metal ions.

45. The waterless composition of claim 41, wherein the chelating agent is selected from the group consisting of ethylenediaminetetraacetic acid ("EDTA") and salts thereof, disodium EDTA, tetrasodium EDTA, calcium disodium EDTA; diethylenetriaminepentaacetic acid ("DTPA") and salts thereof; hydroxyethylethylenediaminetriacetic acid ("HEDTA") and salts thereof; and nitrilotriacetic acid ("NTA") and salts thereof; acetyl trihexyl citrate, aminotrimethylene phosphonic acid, beta-alanine diacetic acid, bismuth citrate, calcium disodium edta, citric acid, cyclohexanediamine tetraacetic acid, diammonium citrate, dibutyl oxalate, diethyl oxalate, diisobutyl oxalate, diisopropyl oxalate, dilithium oxalate, dimethyl oxalate, dipotassium edta, dipotassium oxalate, dipropyl oxalate, disodium edta, disodium edta-copper, disodium pyrophosphate, edta, etidronic acid, hedta, methyl cyclodextrin, oxalic acid, pentapotassium, triphosphate, pentasodium aminotrimethylene phosphonate, pentasodium pentetate, pentasodium triphosphate, pentetic acid, phytic acid, potassium citrate, sodium citrate, sodium dihydroxyethylglycinate, sodium gluceptate, sodium gluconate, sodium hexametaphosphate, sodium metaphosphate, sodium metasilicate, sodium oxalate, sodium trimetaphosphate, tea-edta, tetrahydroxypropyl ethylenediamine, tetrapotassium etidronate, tetrapotassium pyrophosphate, tetrasodium edta, tetrasodium etidronate, tetrasodium pyrophosphate, tripotassium edta, trisodium edta, trisodium hedta, trisodium nta, trisodium phosphate, malic acid,

fumaric acid, maltol, succimer, penicillamine, dimercaprol, and desferrioxamine mesilate.

46. A waterless carrier for use with one or more active agents comprising

- a) a modulating agent; 5
- b) a polyol;
- c) a surface active agent;
- d) a foam adjuvant; and
- e) a liquefied or compressed gas propellant at a concentration of about 3% to about 25% by weight of the composition 10

wherein at least one active agent if present is susceptible to one or more of reaction, breakdown, ionization or oxidation;

wherein the modulating agent comprises an effective 15 amount of one or more agents that are capable of impeding said destabilization and or are capable of stabilizing the active agent primarily by modulating or adjusting the artificial pH of the carrier such that the modulating agent is capable of producing in the waterless carrier an artificial pH or an artificial pH buffering effect at about a pH 20 or pH range in which the stability of at least one active agent is improved when compared to its stability in the carrier without the modulating agent and or by chelating a metal ion such that the modulating agent is capable of 25 reducing in the waterless carrier the availability of metal ions so the stability of at least one active agent is improved when compared to its stability in the carrier without the modulating agent; and

wherein the composition is stored in an aerosol container 30 and upon release expands to form a breakable foam.

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